

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



20

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification 6 :</b> C07D 233/00, 235/02, 401/04, 403/04, A61K 31/44, 31/47, 31/415, 31/505		A1	<b>(11) International Publication Number:</b> WO 96/21654 <b>(43) International Publication Date:</b> 18 July 1996 (18.07.96)
<b>(21) International Application Number:</b> PCT/US96/01094 <b>(22) International Filing Date:</b> 11 January 1996 (11.01.96)		<b>(74) Agents:</b> DINNER, Dara, L. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).	
<b>(30) Priority Data:</b> 08/372,521 12 January 1995 (12.01.95) US 08/374,278 18 January 1995 (18.01.95) US 08/483,348 7 June 1995 (07.06.95) US		<b>(81) Designated States:</b> AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, PT, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
<b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US 08/483,348 (CIP) Filed on 7 June 1995 (07.06.95)		<b>Published</b> With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
<b>(71) Applicant (for all designated States except US):</b> SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property, UW 2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).			
<b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> ADAMS, Jerry, Leroy [US/US]; 611 Forest Road, Wayne, PA 19087 (US). GARIGIPATI, Ravi, Shanker [IN/US]; 5 Flintlock Lane, Wayne, PA 19087 (US). LEE, John, Cheung-Lun [US/US]; 504 Annadale Drive, Berwyn, PA 19312 (US).			
<b>(54) Title:</b> NOVEL COMPOUNDS			
<b>(57) Abstract</b> <p>This invention relates to 1-cycloalkyl, 4,5-trisubstituted imidazole compounds, process for the preparation thereof, the use thereof in treating cytokine mediated diseases and pharmaceutical compositions for the use in such therapy.</p>			
Atty. Docket No. 3015/6/US Serial No. 10/021,780 Anantanarayan et al. Reference 20 of 77			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MK	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

## NOVEL COMPOUNDS

This invention relates to a novel group of imidazole compounds, processes for the preparation thereof, the use thereof in treating cytokine mediated diseases and pharmaceutical compositions for use in such therapy.

### BACKGROUND OF THE INVENTION

Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are biological substances produced by a variety of cells, such as monocytes or macrophages. IL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g., Dinarello et al., *Rev. Infect. Disease*, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic  $\beta$  cells.

Dinarello, *J. Clinical Immunology*, 5 (5), 287-297 (1985), reviews the biological activities which have been attributed to IL-1. It should be noted that some of these effects have been described by others as indirect effects of IL-1.

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosclerosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, 10 scar tissue formation, Crohn's disease, ulcerative colitis, or pyrexia.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified. i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T Cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit 20 HIV gene expression and/or HIV replication. Monokines, specifically TNF, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with monokine activity such as by inhibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby 25 reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T-cells, are targets for viral replication and the level of viral replication is dependent 30 upon the activation state of the cells. [See Rosenberg *et al.*, The Immunopathogenesis of HIV Infection. Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli. *et al.*, Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for 35 T-cells.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, and the herpes virus for similar reasons as those noted.

Interleukin-8 (IL-8) is a chemotactic factor first identified and characterized in 1987. IL-8 is produced by several cell types including mononuclear cells, fibroblasts, endothelial cells, and keratinocytes. Its production from endothelial cells is induced by IL-1, TNF, or lipopolysaccharide (LPS). Human IL-8 has been shown to act on Mouse, 5 Guinea Pig, Rat, and Rabbit Neutrophils. Many different names have been applied to IL-8, such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor.

IL-8 stimulates a number of functions in vitro. It has been shown to have 10 chemoattractant properties for neutrophils, T-lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as well as lysozymal enzyme release and respiratory burst from neutrophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis, this may contribute to increased adhesion of the 15 neutrophils to vascular endothelial cells. Many diseases are characterized by massive neutrophil infiltration. Conditions associated with an increased in IL-8 production (which is responsible for chemotaxis of neutrophil into the inflammatory site) would benefit by compounds which are suppressive of IL-8 production.

IL-1 and TNF affect a wide variety of cells and tissues and these cytokines as 20 well as other leukocyte derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

There remains a need for treatment, in this field, for compounds which are 25 cytokine suppressive anti-inflammatory drugs, i.e. compounds which are capable of inhibiting cytokines, such as IL-1, IL-6, IL-8 and TNF.

#### SUMMARY OF THE INVENTION

This invention relates to the novel compounds of Formula (I) and 30 pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable diluent or carrier.

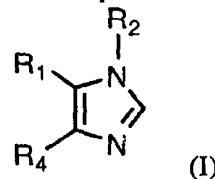
This invention also relates to a method of inhibiting cytokines and the treatment of a cytokine mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I).

This invention more specifically relates to a method of inhibiting the production 35 of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

This invention more specifically relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

5 This invention more specifically relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

Accordingly, the present invention provides for a compound of the Formula :



wherein

10 R<sub>1</sub> is 4-pyridyl, pyrimidinyl, quinolyl, isoquinoliny, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl, which ring is optionally substituted with one or two substituents each of which is independently selected from C<sub>1</sub>-4 alkyl, halogen, hydroxyl, C<sub>1</sub>-4 alkoxy, C<sub>1</sub>-4 alkylthio, C<sub>1</sub>-4 alkylsulfinyl, CH<sub>2</sub>OR<sub>12</sub>, amino, mono and di- C<sub>1</sub>-6 alkyl substituted amino, N(R<sub>10</sub>)C(O)R<sub>c</sub> or an N-heterocycl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>15</sub>;

15 R<sub>4</sub> is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, -C(Z)NR<sub>7</sub>R<sub>17</sub>, -C(Z)OR<sub>16</sub>, -(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>COR<sub>12</sub>, -SR<sub>5</sub>, -SOR<sub>5</sub>, -OR<sub>12</sub>, halo-substituted-C<sub>1</sub>-4 alkyl, C<sub>1</sub>-4 alkyl, -ZC(Z)R<sub>12</sub>, -NR<sub>10</sub>C(Z)R<sub>16</sub>, or -(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>NR<sub>10</sub>R<sub>20</sub> and which, for other positions of substitution, is halogen, cyano, -C(Z)NR<sub>13</sub>R<sub>14</sub>, -C(Z)OR<sub>3</sub>, -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>"COR<sub>3</sub>, -S(O)<sub>m</sub>R<sub>3</sub>, -OR<sub>3</sub>, halo-substituted-C<sub>1</sub>-4 alkyl, -C<sub>1</sub>-4 alkyl, -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>"NR<sub>10</sub>C(Z)R<sub>3</sub>, -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>8</sub>, -NR<sub>10</sub>S(O)<sub>m</sub>'NR<sub>7</sub>R<sub>17</sub>, -ZC(Z)R<sub>3</sub> or -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>"NR<sub>13</sub>R<sub>14</sub>;

20 v is 0, or an integer having a value of 1 or 2;

m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2;

m" is 0, or an integer having a value of 1 to 5;

25 R<sub>c</sub> is hydrogen, C<sub>1</sub>-6 alkyl, C<sub>3</sub>-7 cycloalkyl, aryl, arylC<sub>1</sub>-4 alkyl, heteroaryl, heteroarylC<sub>1</sub>-4alkyl, heterocycl, or heterocyclC<sub>1</sub>-4alkyl C<sub>1</sub>-4 alkyl;

R<sub>2</sub> is an optionally substituted C<sub>3</sub>-7 cycloalkyl, or C<sub>3</sub>-7cycloalkylC<sub>1</sub>-10 alkyl;

R<sub>3</sub> is heterocycl, heterocyclC<sub>1</sub>-10 alkyl or R<sub>8</sub>;

30 R<sub>5</sub> is hydrogen, C<sub>1</sub>-4 alkyl, C<sub>2</sub>-4 alkenyl, C<sub>2</sub>-4 alkynyl or NR<sub>7</sub>R<sub>17</sub>, excluding the moieties -SR<sub>5</sub> being -SNR<sub>7</sub>R<sub>17</sub> and -SOR<sub>5</sub> being -SOH;

35

R<sub>7</sub> and R<sub>17</sub> is each independently selected from hydrogen or C<sub>1</sub>-4 alkyl or R<sub>7</sub> and R<sub>17</sub> together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>15</sub>;

5 R<sub>8</sub> is C<sub>1</sub>-10 alkyl, halo-substituted C<sub>1</sub>-10 alkyl, C<sub>2</sub>-10 alkenyl, C<sub>2</sub>-10 alkynyl, C<sub>3</sub>-7 cycloalkyl, C<sub>5</sub>-7 cycloalkenyl, aryl, arylC<sub>1</sub>-10 alkyl, heteroaryl, heteroarylC<sub>1</sub>-10 alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NHS(O)<sub>2</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>13</sub>R<sub>14</sub>; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

10 n is an integer having a value of 1 to 10;  
R<sub>9</sub> is hydrogen, -C(Z)R<sub>11</sub> or optionally substituted C<sub>1</sub>-10 alkyl, S(O)<sub>2</sub>R<sub>18</sub>, optionally substituted aryl or optionally substituted aryl-C<sub>1</sub>-4 alkyl;  
R<sub>10</sub> and R<sub>20</sub> is each independently selected from hydrogen or C<sub>1</sub>-4 alkyl;  
R<sub>11</sub> is hydrogen, or R<sub>18</sub>;

15 R<sub>12</sub> is hydrogen or R<sub>16</sub>;  
R<sub>13</sub> and R<sub>14</sub> is each independently selected from hydrogen or optionally substituted C<sub>1</sub>-4 alkyl, optionally substituted aryl or optionally substituted aryl-C<sub>1</sub>-4 alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>;

20 R<sub>15</sub> is hydrogen, C<sub>1</sub>-4 alkyl or C(Z)-C<sub>1</sub>-4 alkyl;  
R<sub>16</sub> is C<sub>1</sub>-4 alkyl, halo-substituted-C<sub>1</sub>-4 alkyl, or C<sub>3</sub>-7 cycloalkyl;  
R<sub>18</sub> is C<sub>1</sub>-10 alkyl, C<sub>3</sub>-7 cycloalkyl, heterocyclyl, aryl, arylC<sub>1</sub>-10 alkyl, heterocyclyl, heterocyclyl-C<sub>1</sub>-10alkyl, heteroaryl or heteroarylalkyl;

25 or a pharmaceutically acceptable salt thereof.

#### DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than humans, in need of inhibition of cytokine inhibition or production. In particular, cytokine mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted herein in the Methods of Treatment section, but in particular viral infections. Examples of such viruses include, but are not limited to, lentivirus infections such as, equine infectious anaemia virus, caprine arthritis virus, visna virus, or maedi virus or retrovirus infections, such as but not limited to feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus or other retroviral infections.

In Formula (I), suitable R<sub>1</sub> moieties includes 4-pyridyl, 4-pyrimidinyl, 4-quinolyl, 6-isoquinoliny, 4-quinazolinyl, 1-imidazolyl and 1-benzimidazolyl, of which

the 4-pyridyl, 4-pyrimidinyl and 4-quinolyl are preferred. More preferred is an optionally substituted 4-pyrimidinyl or optionally substituted 4-pyridyl moiety, and most preferred is an optionally substituted 4-pyrimidinyl ring.

Suitable substituents for the R<sub>1</sub> heteroaryl rings are C<sub>1</sub>-4 alkyl, halo, OH, C<sub>1</sub>-4 alkoxy, C<sub>1</sub>-4 alkylthio, C<sub>1</sub>-4 alkylsulfinyl, CH<sub>2</sub>OR<sub>12</sub>, amino, mono and di-C<sub>1</sub>-6 alkyl substituted amino, N(R<sub>10</sub>)C(O)R<sub>c</sub>, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>15</sub>. A preferred substituent for all the R<sub>1</sub> moieties is C<sub>1</sub>-4 alkyl, in particular methyl, amino, and mono- and di-C<sub>1</sub>-6 alkylsubstituted amino, preferably where the amino group is mono-substituted, more preferably with methyl. The alkyl group in the mono- and di-C<sub>1</sub>-6 alkylsubstituted moiety may be halo substituted, such as in trifluoro- i.e., trifluoromethyl or trifluoroethyl.

When the R<sub>1</sub> optional substituent is N(R<sub>10</sub>)C(O) R<sub>c</sub>, wherein R<sub>c</sub> is hydrogen, C<sub>1</sub>-6 alkyl, C<sub>3</sub>-7 cycloalkyl, aryl, arylC<sub>1</sub>-4 alkyl, heteroaryl, heteroarylC<sub>1</sub>-4alkyl, heterocyclyl, or heterocyclylC<sub>1</sub>-4alkyl C<sub>1</sub>-4 alkyl, R<sub>c</sub> is preferably C<sub>1</sub>-6 alkyl; preferably R<sub>10</sub> is hydrogen. It is also recognized that the R<sub>c</sub> moieties, in particular the C<sub>1</sub>-6 alkyl group may be optionally substituted, preferably from one to three times, preferably with halogen, such as fluorine, as in trifluoromethyl or trifluoroethyl.

Preferably, the preferred substituent for R<sub>1</sub> is the amino or mono C<sub>1</sub>-6 alkyl substituted moiety. A preferred ring placement of the R<sub>1</sub> substituent on the 4-pyridyl derivative is the 2-position, such as 2-methyl-4-pyridyl. A preferred ring placement on the 4-pyrimidinyl ring is also at the 2-position, such as in 2-methyl-pyrimidinyl, 2-amino pyrimidinyl or 2-methylaminopyrimidinyl.

Suitably, R<sub>4</sub> is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents. More preferably R<sub>4</sub> is a phenyl or naphthyl ring. Suitable substitutions for R<sub>4</sub> when this is a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl moiety are one or two substituents each of which are independently selected from halogen, -SR<sub>5</sub>, -SOR<sub>5</sub>, -OR<sub>12</sub>, CF<sub>3</sub>, or -(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>NR<sub>10</sub>R<sub>20</sub>, and for other positions of substitution on these rings preferred substitution is halogen, -S(O)<sub>m</sub>R<sub>3</sub>, -OR<sub>3</sub>, CF<sub>3</sub>, -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>"NR<sub>13</sub>R<sub>14</sub>, -NR<sub>10</sub>C(Z)R<sub>3</sub> and -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>8</sub>. Preferred substituents for the 4-position in phenyl and naphth-1-yl and on the 5-position in naphth-2-yl include halogen, especially fluoro and chloro and -SR<sub>5</sub> and -SOR<sub>5</sub> wherein R<sub>5</sub> is preferably a C<sub>1</sub>-2 alkyl, more preferably methyl; of which the fluoro and chloro is more preferred, and most especially preferred is fluoro. Preferred substituents for the 3-position in phenyl and naphth-1-yl rings include: halogen, especially fluoro and chloro; -OR<sub>3</sub>, especially C<sub>1</sub>-4 alkoxy; CF<sub>3</sub>, NR<sub>10</sub>R<sub>20</sub>, such as amino; -NR<sub>10</sub>C(Z)R<sub>3</sub>, especially -NHCO(C<sub>1</sub>-10 alkyl); -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>8</sub>, especially -NHSO<sub>2</sub>(C<sub>1</sub>-10 alkyl), and -SR<sub>3</sub> and -SOR<sub>3</sub> wherein R<sub>3</sub> is preferably a C<sub>1</sub>-2

alkyl, more preferably methyl. When the phenyl ring is disubstituted preferably it is two independent halogen moieties, such as fluoro and chloro, preferably di-chloro and more preferably in the 3, 4-position. It is also preferred that for the 3-position of both the -OR<sub>3</sub> and -ZC(Z)R<sub>3</sub> moieties, R<sub>3</sub> may also include hydrogen.

5 Preferably, the R<sub>4</sub> moiety is an unsubstituted or substituted phenyl moiety. More preferably, R<sub>4</sub> is phenyl or phenyl substituted at the 4-position with fluoro and/or substituted at the 3-position with fluoro, chloro, C<sub>1-4</sub> alkoxy, methane-sulfonamido or acetamido, or R<sub>4</sub> is a phenyl di-substituted at the 3,4-position independently with chloro or fluoro, more preferably chloro. Most preferably, R<sub>4</sub> is a 4-fluorophenyl.

10 In Formula (I), Z is suitably oxygen.

Suitably, R<sub>2</sub> is an optionally substituted C<sub>3-7</sub>cycloalkyl, or an optionally substituted C<sub>3-7</sub>cycloalkyl C<sub>1-10</sub> alkyl. Preferably R<sub>2</sub> is a C<sub>3-7</sub>cycloalkyl, of which the cycloalkyl group is preferably a C<sub>4-7</sub> ring, more preferably a C<sub>4</sub> or C<sub>6</sub> ring, most preferably a C<sub>6</sub> ring, which ring is optionally substituted.

15 The C<sub>3-7</sub>cycloalkyl ring may substituted one to three times independently by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; C<sub>1-10</sub> alkoxy, such as methoxy or ethoxy; S(O)<sub>m</sub> alkyl, wherein m is 0, 1, or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; S(O)<sub>m</sub> aryl; cyano; nitro; amino, mono & di-substituted amino, such as in the NR<sub>7</sub>R<sub>17</sub> group, wherein R<sub>7</sub> and R<sub>17</sub> are as defined in Formula (I); or where the R<sub>7</sub>R<sub>17</sub> may cyclize together with the nitrogen to which they are attached to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from oxygen, sulfur or NR<sub>15</sub> (and R<sub>15</sub> is as defined for Formula (I)): N(R<sub>10</sub>)C(O)X<sub>1</sub> (wherein R<sub>10</sub> is as defined for Formula (I)), and X<sub>1</sub> is C<sub>1-4</sub> alkyl, aryl or arylC<sub>1-4</sub>alkyl; N(R<sub>10</sub>)C(O) aryl; C<sub>1-10</sub> alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; optionally substituted alkyl wherein the substituents are halogen, (such as CF<sub>3</sub>), hydroxy, nitro, cyano, amino, mono & di-substituted amino, such as in the NR<sub>7</sub>R<sub>17</sub> group, S(O)<sub>m</sub> alkyl and S(O)<sub>m</sub> aryl, wherein m is 0, 1 or 2; optionally substituted C<sub>1-10</sub>alkylene, such as ethylene or propylene; optionally substituted C<sub>1-10</sub> alkyne, such as acetylene (ethynyl) or 1-propynyl; C(O)OR<sub>11</sub> (wherein R<sub>11</sub> is as defined in Formula (I)), such as the free acid or methyl ester derivative; the group R<sub>a</sub>; -C(O)H; =O; =N-OR<sub>11</sub>; -N(H)-OH (or substituted alkyl or aryl derivatives thereof on the nitrogen or the oxime moiety); -N(OR<sub>b</sub>)-C(O)-R<sub>6</sub>; oxirane; an optionally substituted aryl, such as phenyl; an optionally substituted arylC<sub>1-4</sub>alkyl, such as benzyl or phenethyl; an optionally substituted heterocycle or heterocyclic C<sub>1-4</sub>alkyl, and further these aryl, arylalkyl, heterocyclic, and heterocyclic alkyl moieties are optionally substituted one to two times by halogen, hydroxy, C<sub>1-10</sub> alkoxy, S(O)<sub>m</sub> alkyl, cyano, nitro, amino, mono & di-substituted amino, such as in the NR<sub>7</sub>R<sub>17</sub> group, an alkyl, halosubstituted alkyl.

Suitably  $R_a$  is a 1,3-dioxyalkylene group of the formula  $-O-(CH_2)_s-O-$ , wherein  $s$  is 1 to 3, preferably  $s$  is 2 yielding a 1,3-dioxyethylene moiety.

Suitably  $R_b$  is hydrogen, a pharmaceutically acceptable cation, aroyl or a C1-10 alkanoyl group.

5      Suitably  $R_6$  is  $NR_{19}R_{21}$ ; alkyl 1-6; halosubstituted alkyl 1-6; hydroxy substituted alkyl 1-6; alkenyl 2-6; aryl or heteroaryl optionally substituted by halogen, alkyl 1-6, halosubstituted alkyl 1-6, hydroxyl, or alkoxy 1-6.

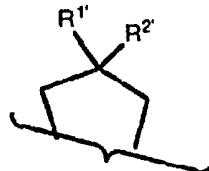
Suitably  $R_{19}$  is H or alkyl 1-6.

10     Suitably  $R_{21}$  is H, alkyl 1-6, aryl, benzyl, heteroaryl, alkyl substituted by halogen or hydroxyl, or phenyl substituted by a member selected from the group consisting of halo, cyano, alkyl 1-12, alkoxy 1-6, halosubstituted alkyl 1-6, alkylthio, alkylsulphonyl, or alkylsulfinyl; or  $R_{19}$  and  $R_{21}$  may together with the nitrogen to which they are attached form a ring having 5 to 7 members, which members may be optionally replaced by a heteroatom selected from oxygen, sulfur or nitrogen. The ring 15 may be saturated or contain more than one unsaturated bond. Preferably  $R_6$  is  $NR_{19}R_{21}$  and  $R_{19}$  and  $R_{21}$  are preferably hydrogen.

When the  $R_2$  moiety is substituted by  $NR_7R_{17}$  group, or  $NR_7R_{17}$  C1-10 alkyl group, and the  $R_7$  and  $R_{17}$  areas defined in Formula (I), the substituent is preferably an amino, amino alkyl, or an optionally substituted pyrrolidinyl moiety.

20     A preferred ring placement on the cyclohexyl ring, particularly when it is a C6 ring, is the 4-position.

When the cyclohexyl ring is disubstituted it is preferably disubstituted at the 4 position, such as in:



25     wherein  $R^{1'}$  and  $R^{2'}$  are independently the optional substituents indicated above for  $R_2$ . Preferably,  $R^{1'}$  and  $R^{2'}$  are hydrogen, hydroxy, alkyl, substituted alkyl, optionally substituted alkynyl, aryl, arylalkyl,  $NR_7R_{17}$ , and  $N(R_{10})C(O)R_{11}$ . Suitably, alkyl is C1-4 alkyl, such as methyl, ethyl, or isopropyl;  $NR_7R_{17}$  and  $NR_7R_{17}$  alkyl, such as amino, methylamino, aminomethyl, aminoethyl; substituted alkyl such as in 30 cyanomethyl, cyanoethyl, nitroethyl, pyrrolidinyl; optionally substituted alkynyl, such as propynyl or ethynyl; aryl such as in phenyl; arylalkyl, such as in benzyl; or together  $R^{1'}$  and  $R^{2'}$  are a keto functionality.

As used herein, "optionally substituted" unless specifically defined herein, shall 35 mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy;

hydroxy substituted C<sub>1</sub>-10alkyl; C<sub>1</sub>-10 alkoxy, such as methoxy or ethoxy; S(O)<sub>m</sub> alkyl, wherein m is 0, 1 or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR<sub>7</sub>R<sub>17</sub> group; or where the R<sub>7</sub>R<sub>17</sub> may together with the nitrogen to which they are attached cyclize to form a 5 to

5 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C<sub>1</sub>-10 alkyl, cycloalkyl, or cycloalkyl alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; halosubstituted C<sub>1</sub>-10 alkyl, such CF<sub>3</sub>; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, wherein these aryl moieties may also be  
10 substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C<sub>1</sub>-10 alkoxy; S(O)<sub>m</sub> alkyl; amino, mono & di-substituted amino, such as in the NR<sub>7</sub>R<sub>17</sub> group; alkyl, or CF<sub>3</sub>.

In a preferred subgenus of compounds of Formula (I), R<sub>1</sub> is 4-pyridyl, 2-alkyl-4-pyridyl, 4-pyrimidinyl, 2-amino-4-pyrimidinyl or 2-methylamino-4-pyrimidinyl; R<sub>2</sub> is an optionally substituted C<sub>4</sub> or C<sub>6</sub> cycloalkyl and R<sub>4</sub> is phenyl or optionally substituted phenyl. In a more preferred subgenus R<sub>4</sub> is phenyl or phenyl substituted one or two times by fluoro, chloro, C<sub>1</sub>-4 alkoxy, -S(O)<sub>m</sub> alkyl, methanesulfonamido or acetamido; R<sub>2</sub> is cyclohexyl substituted by methyl, phenyl, benzyl, amino, acetamide, aminomethyl, 20 aminoethyl, cyanomethyl, cyanoethyl, hydroxy, nitroethyl, pyrrolidinyl, ethynyl, 1-propynyl, =O, O-(CH<sub>2</sub>)<sub>2</sub>O-, =NOR<sub>11</sub>, wherein R<sub>11</sub> is hydrogen, alkyl or aryl, NHOH, or N(OH)-C(O)-NH<sub>2</sub>; and R<sub>1</sub> is a 4-pyrimidinyl moiety, optionally substituted by amino, or methylamino; or R<sub>1</sub> is a 4-pyridyl optionally substituted by methyl.

25 Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of 30 Formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

35

The following terms, as used herein, refer to:

- "halo" or "halogens", include the halogens: chloro, fluoro, bromo and iodo.

- "C<sub>1-10</sub>alkyl" or "alkyl" - both straight and branched chain radicals of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- 5       • The term "cycloalkyl" is used herein to mean cyclic radicals, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- 10      • The term "cycloalkenyl" is used herein to mean cyclic radicals, preferably of 5 to 8 carbons, which have at least one bond including but not limited to cyclopentenyl, cyclohexenyl, and the like.
- 15      • The term "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-but enyl, 2-but enyl and the like.
- 20      • "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.
- 25      • "heterocyclic" (on its own or in any combination, such as "heterocyclalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S: such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyran, or imidazolidine.
- 30      • The term "aralkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C<sub>1-4</sub> alkyl as defined above attached to an aryl, heteroaryl or heterocyclic moiety as also defined herein unless otherwise indicate.
- "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized S(O)<sub>2</sub> moiety.
- "aryl" - a C(O)Ar, wherein Ar is as phenyl, naphthyl, or aryl alkyl derivative such as defined above, such group include but are note limited to benzyl and phenethyl.
- "alkanoyl" - a C(O)C<sub>1-10</sub> alkyl wherein the alkyl is as defined above.
- 35      It is recognized that the compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

Exemplified compounds of Formula (I) include:

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-(1,3-dioxycyclopentyl) cyclohexyl) imidazole;

5 5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-ketocyclohexyl)imidazole;

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-cyclohexyl oxime) imidazole;

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-cyclohexyl hydroxylamine) imidazole;

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(*trans*-4-hydroxyurea) imidazole;

10 5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(*cis*-4-hydroxyurea) imidazole;

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-hydroxycyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-ketocyclohexyl)- imidazole;

15 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(*trans*-4-hydroxy- cyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(*cis*-4-hydroxy- cyclohexyl)imidazole;

5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-(*cis*-pyrrolidinyl)- cyclohexyl]imidazole;

20 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-(*trans*-1-pyrrolidinyl)- cyclohexyl]imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-ethynyl-4-hydroxy- cyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-(1-propynyl)-4- hydroxycyclohexyl)imidazole;

25 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-amino-4-methyl- cyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-acetamido-4-methyl- cyclohexyl)imidazole;

30 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-methyl- cyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-oxiranyl- cyclohexyl)imidazole;

5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-cyanomethyl-4- hydroxycyclohexyl)imidazole;

35 5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4- hydroxymethylcyclohexyl)imidazole;

5-[4-(2-Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-hydroxy-4-(1-propynyl)-cyclohexyl]imidazole;

5-[4-(2-Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-methyl-cyclohexyl)imidazole

5

Additional compounds within the scope of Formula (I) include:

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-isopropyl-cyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-phenyl-cyclohexyl)imidazole;

10

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-benzyl-cyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-cyanomethyl-cyclohexyl)imidazole;

15

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-(2-cyanoethyl)cyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-(2-aminoethyl)cyclohexyl)imidazole;

20

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-(2-nitroethyl)-cyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxymethyl-4-amino-cyclohexyl)imidazole.

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-amino-cyclohexyl)imidazole;

25

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-amino-cyclohexyl)imidazole.

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-thiomethyl-cyclohexyl)imidazole.

30

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-hydroxy-methylcyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-aminomethyl-cyclohexyl)imidazole;

5-[4-(2-amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-amino-4-methyl-cyclohexyl)imidazole;

35

5-[4-(2-amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-methyl-cyclohexyl)imidazole;

5-[4-(2-amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-oxiranyl-cyclohexyl)imidazole.

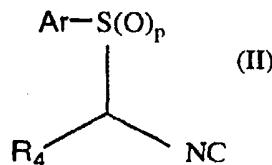
Exemplified and additional compounds of Formula (I) included herein include the 2-methylamino-4-pyrimidinyl derivatives of the 2-aminopyrimidin-4-yl compounds noted above noted compounds and the 2-amino-4-pyrimidinyl derivatives of the 2-  
5 methylaminopyrimidin-4-yl compounds noted above where not where not explicitly described.

The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in Schemes I to XI below. The synthesis provided for in these Schemes is applicable for the producing compounds of Formula (I)  
10 having a variety of different R<sub>1</sub>, R<sub>2</sub>, and R<sub>4</sub> groups which are reacted, employing optional substituents which are suitably protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. Once the imidazole nucleus has been established, further compounds of Formula (I) may be prepared by applying standard  
15 techniques for functional group interconversion, well known in the art.

For instance: -C(O)NR<sub>13</sub>R<sub>14</sub> from -CO<sub>2</sub>CH<sub>3</sub> by heating with or without catalytic metal cyanide, e.g. NaCN, and HNR<sub>13</sub>R<sub>14</sub> in CH<sub>3</sub>OH; -OC(O)R<sub>3</sub> from -OH with e.g., ClC(O)R<sub>3</sub> in pyridine; -NR<sub>10</sub>-C(S)NR<sub>13</sub>R<sub>14</sub> from -NHR<sub>10</sub> with an alkylisothiocyanate or thiocyanic acid; NR<sub>6</sub>C(O)OR<sub>6</sub> from -NHR<sub>6</sub> with the alkyl  
20 chloroformate: -NR<sub>10</sub>C(O)NR<sub>13</sub>R<sub>14</sub> from -NHR<sub>10</sub> by treatment with an isocyanate, e.g. HN=C=O or R<sub>10</sub>N=C=O; -NR<sub>10</sub>-C(O)R<sub>8</sub> from -NHR<sub>10</sub> by treatment with Cl-  
C(O)R<sub>3</sub> in pyridine: -C(=NR<sub>10</sub>)NR<sub>13</sub>R<sub>14</sub> from -C(NR<sub>13</sub>R<sub>14</sub>)SR<sub>3</sub> with H<sub>3</sub>NR<sub>3</sub><sup>+</sup>OAc<sup>-</sup> by heating in alcohol; -C(NR<sub>13</sub>R<sub>14</sub>)SR<sub>3</sub> from -C(S)NR<sub>13</sub>R<sub>14</sub> with R<sub>6</sub>-I in an inert solvent, e.g. acetone: -C(S)NR<sub>13</sub>R<sub>14</sub> (where R<sub>13</sub> or R<sub>14</sub> is not hydrogen) from  
25 -C(S)NH<sub>2</sub> with HNR<sub>13</sub>R<sub>14</sub>-C(=NCN)-NR<sub>13</sub>R<sub>14</sub> from -C(=NR<sub>13</sub>R<sub>14</sub>)-SR<sub>3</sub> with NH<sub>2</sub>CN by heating in anhydrous alcohol, alternatively from -C(=NH)-NR<sub>13</sub>R<sub>14</sub> by treatment with BrCN and NaOEt in EtOH; -NR<sub>10</sub>-C(=NCN)SR<sub>8</sub> from -NHR<sub>10</sub> by treatment with (R<sub>8</sub>S)<sub>2</sub>C=NCN; -NR<sub>10</sub>SO<sub>2</sub>R<sub>3</sub> from -NHR<sub>10</sub> by treatment with  
30 ClSO<sub>2</sub>R<sub>3</sub> by heating in pyridine; -NR<sub>10</sub>C(S)R<sub>3</sub> from -NR<sub>10</sub>C(O)R<sub>8</sub> by treatment with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide]; -NR<sub>10</sub>SO<sub>2</sub>CF<sub>3</sub> from -NHR<sub>6</sub> with triflic anhydride and base wherein R<sub>3</sub>, R<sub>6</sub>, R<sub>10</sub>, R<sub>13</sub> and R<sub>14</sub> are as defined in Formula (I) herein.

In a further aspect the present invention provides for compounds of the Formula  
35 (II) having the structure:

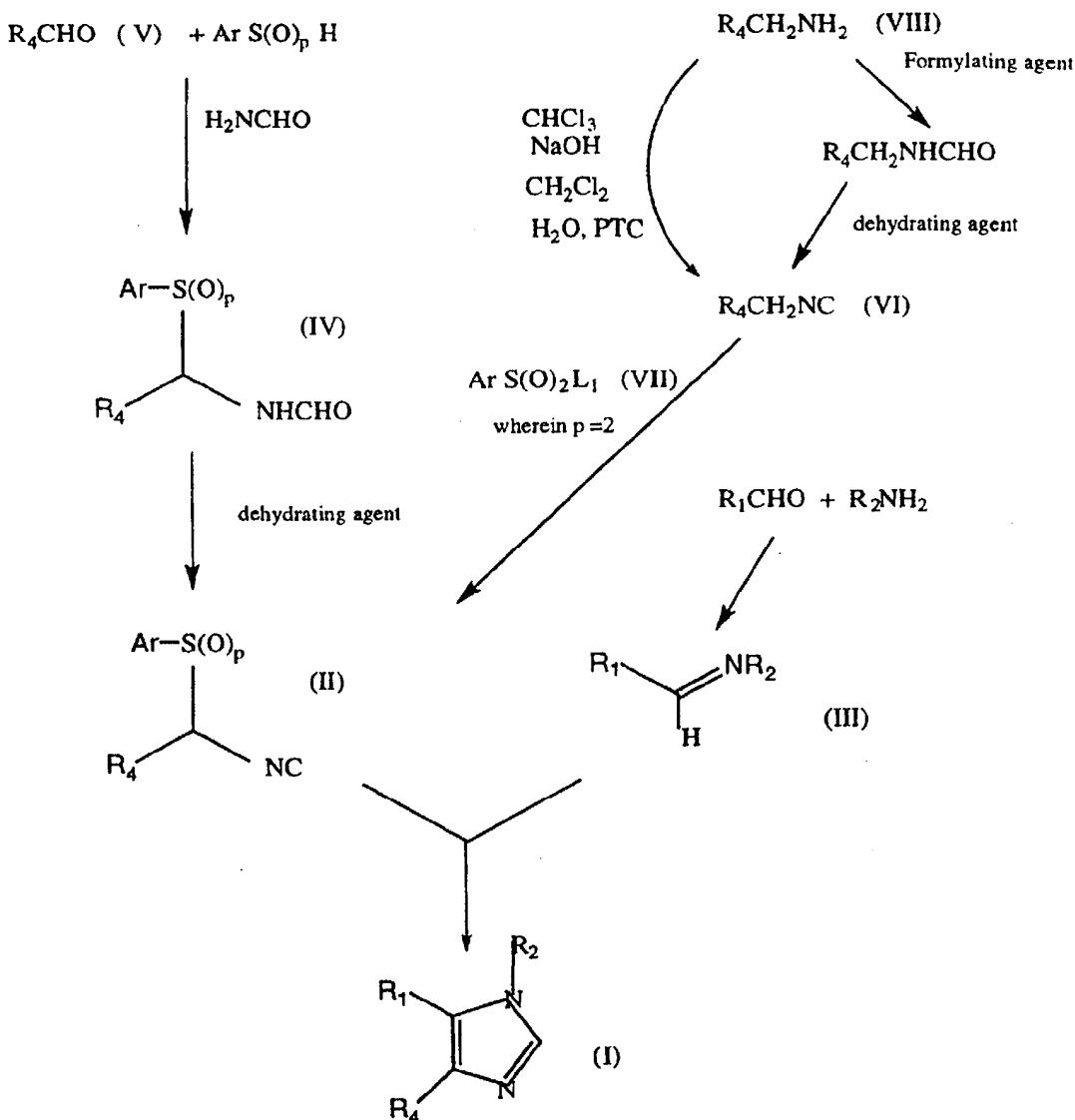
- 14 -



wherein p is 0, or 2; R<sub>4</sub> is as defined for Formula (I) and Ar is an optionally substituted aryl as defined herein. Suitably, Ar is phenyl optionally substituted by C<sub>1-4</sub>alkyl, C<sub>1-4</sub> alkoxy or halo. Preferably Ar is phenyl or 4-methylphenyl, i.e. a tosyl derivative. Compounds of Formula (II) are believed novel, provided than when Ar is tosyl, and p is 0 or 2, then R<sub>4</sub> is not an unsubstituted phenyl.

Precursors of the groups R<sub>1</sub>, R<sub>2</sub> and R<sub>4</sub> can be other R<sub>1</sub>, R<sub>2</sub> and R<sub>4</sub> groups which can be interconverted by applying standard techniques for functional group interconversion. For example a compound of the formula (I) wherein R<sub>2</sub> is halo-<sub>10</sub>substituted C<sub>1-10</sub> alkyl can be converted to the corresponding C<sub>1-10</sub> alkylN<sub>3</sub> derivative by reacting with a suitable azide salt, and thereafter if desired can be reduced to the corresponding C<sub>1-10</sub>alkylNH<sub>2</sub> compound, which in turn can be reacted with R<sub>18</sub>S(O)<sub>2</sub>X wherein X is halo (e.g., chloro) to yield the corresponding C<sub>1-10</sub>alkylNHS(O)<sub>2</sub>R<sub>18</sub> compound.

15 Alternatively a compound of the formula (I) where R<sub>2</sub> is halo-substituted C<sub>1-10</sub>-alkyl can be reacted with an amine R<sub>13</sub>R<sub>14</sub>NH to yield the corresponding C<sub>1-10</sub>-alkylNR<sub>13</sub>R<sub>14</sub> compound, or can be reacted with an alkali metal salt of R<sub>18</sub>SH to yield the corresponding C<sub>1-10</sub>alkylSR<sub>18</sub> compound.



Referring to Scheme I the compounds of Formula (I) are suitably prepared by  
 5 reacting a compound of the Formula (II) with a compound of the Formula (III) wherein p is 0 or 2, R<sub>1</sub>, R<sub>2</sub> and R<sub>4</sub> are as defined herein, for Formula (I), or are precursors of the groups R<sub>1</sub>, R<sub>2</sub> and R<sub>4</sub>, and Ar is an optionally substituted phenyl group, and thereafter if necessary converting a precursor of R<sub>1</sub>, R<sub>2</sub> and R<sub>4</sub> to a group R<sub>1</sub>, R<sub>2</sub> and R<sub>4</sub>. It is recognized that R<sub>2</sub>NH<sub>2</sub> which is reacted with R<sub>1</sub>CHO to form the imine, Formula (III)  
 10 the R<sub>2</sub> moiety when it contains a reactive functional group, such as a primary or secondary amine, an alcohol, or thiol compound the group must be suitably protected. Suitable protecting groups may be found in, Protecting Groups in Organic Synthesis,

Greene T W, Wiley-Interscience, New York, 1981, whose disclosure is incorporated herein by reference. For instance, when  $R_2$  is contains as a substituent group a heterocyclic ring, such as a piperidine ring, the nitrogen is protected with groups such as t-Boc,  $CO_2R$  18, or a substituted arylalkyl moiety.

5

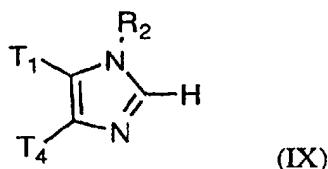
Suitably, the reaction is performed at ambient temperature or with cooling (e.g. -50° to 10°) or heating in an inert solvent such as methylene chloride, DMF, tetrahydrofuran, toluene, acetonitrile, or dimethoxyethane in the presence of an appropriate base such as 1,8-diazabicyclo [5.4.0.] undec-7-ene (DBU) or a guanidine 10 base such as 1,5,7-triaza-bicyclo [4.4.0] dec-5-ene (TBD). The intermediates of formula (II) have been found to be very stable and capable of storage for a long time. Preferably, p is 2.

Reaction a compound of the Formula (II) wherein p = 2, with a compound of the Formula (III)-Scheme I gives consistently higher yields of compounds of Formula 15 (I) than when p=0. In addition, the reaction of Formula (II) compounds wherein p = 2 is more environmentally and economically attractive. When p=0, the preferred solvent used is methylene chloride, which is environmentally unattractive for large scale processing, and the preferred base, TBD, is also expensive, and produces some byproducts and impurities, than when using the commercially attractive synthesis (p=2) 20 as further described herein.

As noted, Scheme I utilizes the 1,3-dipolar cycloadditions of an anion of a substituted aryl thiomethylisocyanide (when p=0) to an imine. More specifically, this reaction requires a strong base, such as an amine base, to be used for the deprotonation step. The commercially available TBD is preferred although t- 25 butoxide,  $Li^+$  or  $Na^+$ , or  $K^+$  hexamethyldisilazide may also be used. While methylene chloride is the prefered solvent, other halogenated solvents, such as chloroform or carbon tetrachloride; ethers, such as THF, DME, DMF, diethylether, t-butyl methyl ether; as well as acetonitrile, toluene or mixtures thereof can be utilized. The reaction may take place from about -20°C to about; 40°C, preferably 30 from about 0°C to about 23°C, more preferably from about 0°C to about 10°C, and most preferably about 4°C for reactions involving an  $R_1$  group of pyrimidine. For compounds wherein  $R_1$  is pyridine, it is recognized that varying the reations conditions of both temperature and solvent may be necessary, such as decreasing temperatures to about -50°C or changing the solvent to THF.

35

In a further process, compounds of Formula (I) may be prepared by coupling a suitable derivative of a compound of Formula (IX):



wherein T<sub>1</sub> is hydrogen and T<sub>4</sub> is R<sub>4</sub>, or alternatively T<sub>1</sub> is R<sub>1</sub> and T<sub>4</sub> is H in which R<sub>1</sub>, R<sub>2</sub> and R<sub>4</sub> are as hereinbefore defined; with: (i) when T<sub>1</sub> is hydrogen, a suitable derivative of the heteroaryl ring R<sub>1</sub>H, under ring coupling conditions, to effect coupling of the heteroaryl ring R<sub>1</sub> to the imidazole nucleus at position 5; (ii) when T<sub>4</sub> is hydrogen, a suitable derivative of the aryl ring R<sub>4</sub>H, under ring coupling conditions, to effect coupling of the aryl ring R<sub>4</sub> to the imidazole nucleus at position 4.

Such aryl/heteroaryl coupling reactions are well known to those skilled in the art. In general, an organometallic synthetic equivalent of an anion of one component is coupled with a reactive derivative of the second component, in the presence of a suitable catalyst. The anion equivalent may be formed from either the imidazole of Formula (IX), in which case the aryl/heteroaryl compound provides the reactive derivative, or the aryl/heteroaryl compound in which case the imidazole provides the reactive derivative. Accordingly, suitable derivatives of the compound of Formula (IX) or the aryl/heteroaryl rings include organometallic derivatives such as organomagnesium, organozinc, organostannane and boronic acid derivatives and suitable reactive derivatives include the bromo, iodo, fluorosulfonate and trifluoromethanesulphonate derivatives. Suitable procedures are described in WO 91/19497, the disclosure of which is incorporated by reference herein.

Suitable organomagnesium and organozinc derivatives of a compound of Formula (IX) may be reacted with a halogen, fluorosulfonate or triflate derivative of the heteroaryl or aryl ring, in the presence of a ring coupling catalyst, such as a palladium (0) or palladium (II) catalyst, following the procedure of Kumada *et al.*, Tetrahedron Letters, 22, 5319 (1981). Suitable such catalysts include *tetrakis*-(triphenylphosphine)palladium and PdCl<sub>2</sub>[1,4-*bis*-(diphenylphosphino)-butane], optionally in the presence of lithium chloride and a base, such as triethylamine. In addition, a nickel (II) catalyst, such as Ni(II)Cl<sub>2</sub>(1,2-biphenylphosphino)ethane, may also be used for coupling an aryl ring, following the procedure of Pridgen *et al.*, J. Org. Chem., 1982, 47, 4319. Suitable reaction solvents include hexamethylphosphor-amide. When the heteroaryl ring is 4-pyridyl, suitable derivatives include 4-bromo- and 4-iodo-pyridine and the fluorosulfonate and triflate esters of 4-hydroxy pyridine. Similarly, suitable derivatives for when the aryl ring is phenyl include the bromo, fluorosulfonate, triflate and, preferably, the iodo-derivatives. Suitable organomagnesium and organozinc derivatives may be obtained by treating a compound

of Formula (IX) or the bromo derivative thereof with an alkyl lithium compound to yield the corresponding lithium reagent by deprotonation or transmetallation, respectively. This lithium intermediate may then be treated with an excess of a magnesium halide or zinc halide to yield the corresponding organometallic reagent.

5        A trialkyltin derivative of the compound of Formula (IX) may be treated with a bromide, fluorosulfonate, triflate, or, preferably, iodide derivative of an aryl or heteroaryl ring compound, in an inert solvent such as tetrahydrofuran, preferably containing 10% hexamethylphosphoramide, in the presence of a suitable coupling catalyst, such as a palladium (0) catalyst, for instance *tetrakis-(triphenylphosphine)-palladium*, by the method described in by Stille, J. Amer. Chem. Soc, 1987, **109**, 5478, US Patents 4,719,218 and 5,002,942, or by using a palladium (II) catalyst in the presence of lithium chloride optionally with an added base such as triethylamine, in an inert solvent such as dimethyl formamide. Trialkyltin derivatives may be conveniently obtained by metallation of the corresponding compound of Formula (IX) with a 10      15      lithiating agent, such as *s*-butyl-lithium or *n*-butyllithium, in an ethereal solvent, such as tetrahydrofuran, or treatment of the bromo derivative of the corresponding compound of Formula (IX) with an alkyl lithium, followed, in each case, by treatment with a trialkyltin halide. Alternatively, the bromo- derivative of a compound of 20      25      Formula (IX) may be treated with a suitable heteroaryl or aryl trialkyl tin compound in the presence of a catalyst such as *tetrakis-(triphenyl-phosphine)-palladium*, under conditions similar to those described above.

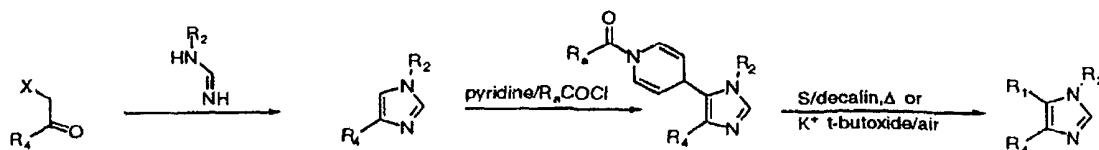
Boronic acid derivatives are also useful. Hence, a suitable derivative of a compound of Formula (IX), such as the bromo, iodo, triflate or fluorosulphonate derivative, may be reacted with a heteroaryl- or aryl-boronic acid, in the presence of a 25      30      palladium catalyst such as *tetrakis-(triphenylphosphine)-palladium* or  $PdCl_2[1,4\text{-}bis\text{-}(diphenyl\text{-}phosphino)\text{-}butane}]$  in the presence of a base such as sodium bicarbonate, under reflux conditions, in a solvent such as dimethoxyethane (see Fischer and Haviniga, Rec. Trav. Chim. Pays Bas, **84**, 439, 1965, Snieckus, V., Tetrahedron Lett., **29**, 2135, 1988 and Terashimia, M., Chem. Pharm. Bull., **11**, 4755, 1985). Non-aqueous conditions, for instance, a solvent such as DMF, at a temperature of about 35      40      100°C, in the presence of a Pd(II) catalyst may also be employed (see Thompson W J *et al.* J Org Chem, **49**, 5237, 1984). Suitable boronic acid derivatives may be prepared by treating the magnesium or lithium derivative with a trialkylborate ester, such as triethyl, tri-*iso*-propyl or tributylborate, according to standard procedures.

35      In such coupling reactions, it will be readily appreciated that due regard must be exercised with respect to functional groups present in the compounds of Formula (IX). Thus, in general, amino and sulfur substituents should be non-oxidised or protected.

Compounds of Formula (IX) are imidazoles and may be obtained by any of the procedures herein before described for preparing compounds of Formula (I). In particular, an  $\alpha$ -halo-ketone or other suitably activated ketones  $R_4COCH_2Hal$  (for compounds of Formula (IX) in which  $T_1$  is hydrogen) or  $R_1COCH_2Hal$  (for 5 compounds of Formula (IX) in which  $T_4$  is hydrogen) may be reacted with an amidine of the formula  $R_2NH-C\equiv NH$ , wherein  $R_2$  is as defined in Formula (I), or a salt thereof, in an inert solvent such as a halogenated hydrocarbon solvent, for instance chloroform, at a moderately elevated temperature, and, if necessary, in the presence of a suitable condensation agent such as a base. The preparation of suitable  $\alpha$ -halo-ketones is 10 described in WO 91/19497. Suitable reactive esters include esters of strong organic acids such as a lower alkane sulphonic or aryl sulphonic acid, for instance, methane or *p*-toluene sulphonic acid. The amidine is preferably used as the salt, suitably the hydrochloride salt, which may then be converted into the free amidine *in situ*, by employing a two phase system in which the reactive ester is in an inert organic solvent 15 such as chloroform, and the salt is in an aqueous phase to which a solution of an aqueous base is slowly added, in dimolar amount, with vigorous stirring. Suitable amidines may be obtained by standard methods, see for instance, Garigipati R, Tetrahedron Letters, 190, 31, 1989.

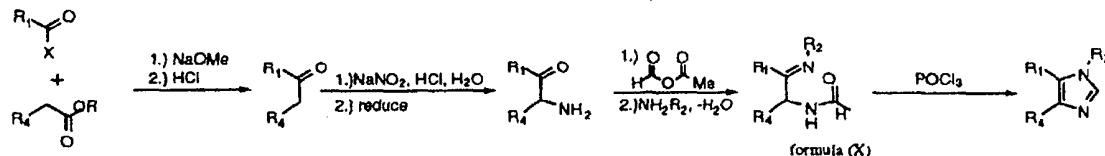
Compounds of Formula (I) may also be prepared by a process which comprises 20 reacting a compound of Formula (IX), wherein  $T_1$  is hydrogen, with an N-acyl heteroaryl salt, according to the method disclosed in US patent 4,803,279; US patent 4,719,218 and US patent 5,002,942, to give an intermediate in which the heteroaryl ring is attached to the imidazole nucleus and is present as a 1,4-dihydro derivative thereof, which intermediate may then be subjected to oxidative-deacylation conditions 25 (Scheme II). The heteroaryl salt, for instance a pyridinium salt, may be either preformed or, more preferably, prepared *in situ* by adding a substituted carbonyl halide (such as an acyl halide, an aroyl halide, an arylalkyl haloformate ester, or, preferably, an alkyl haloformate ester, such as acetyl bromide, benzoylchloride, benzyl chloroformate, or, preferably, ethyl chloroformate) to a solution of the compound of 30 Formula (IX) in the heteroaryl compound  $R_1H$  or in an inert solvent such as methylene chloride to which the heteroaryl compound has been added. Suitable deacylating and oxidising conditions are described in U.S. Patent Nos. 4,803,279, 4,719,218 and 5,002,942, which references are hereby incorporated by reference in their entirety. Suitable oxidizing systems include sulfur in an inert solvent or solvent mixture, such as 35 decalin, decalin and diglyme, *p*-cymene, xylene or mesitylene, under reflux conditions, or, preferably, potassium *t*-butoxide in *t*-butanol with dry air or oxygen.

- 20 -



SCHEME II

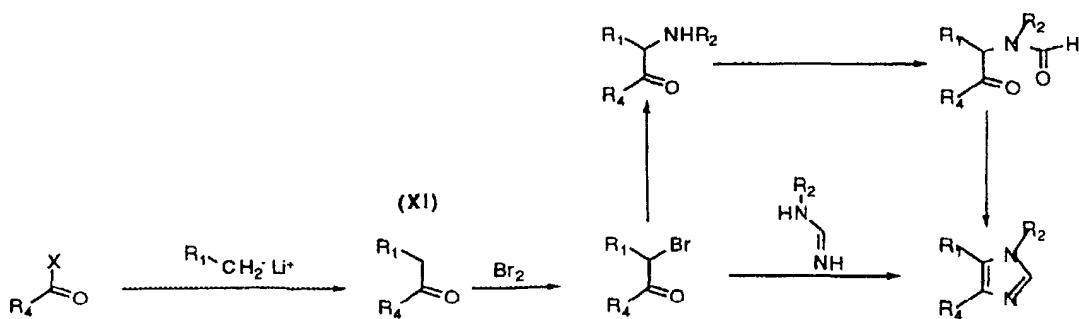
5 In a further process, illustrated in Scheme III below, compounds of Formula (I) may be prepared by treating a compound of Formula (X) thermally or with the aid of a cyclising agent such as phosphorus oxychloride or phosphorus pentachloride (see Engel and Steglich, Liebigs Ann Chem, 1978, 1916 and Strzybny *et al.*, J Org Chem, 1963, 28, 3381). Compounds of Formula (X) may be obtained, for instance, by  
10 acylating the corresponding  $\alpha$ -keto-amine with an activated formate derivative such as the corresponding anhydride, under standard acylating conditions followed by formation of the imine with  $R_2NH_2$ . The aminoketone may be derived from the parent ketone by oxamination and reduction and the requisite ketone may in turn be prepared by decarboxylation of the beta-ketoester obtained from the condensation of an aryl  
15 (heteroaryl) acetic ester with the  $R_1COX$  component.



SCHEME III

20 In Scheme IV illustrated below, two (2) different routes which use ketone (formula XI) for preparing a compound of Formula (I). A heterocyclic ketone (XI) is prepared by adding the anion of the alkyl heterocycle such as 4-methyl-quinoline (prepared by treatment thereof with an alkyl lithium, such as *n*-butyl lithium) to an N-alkyl-O-alkoxybenzamide, ester, or any other suitably activated derivative of the same oxidation state. Alternatively, the anion may be condensed with a benzaldehyde, to  
25 give an alcohol which is then oxidised to the ketone (XI).

- 21 -

SCHEME IV

5 In a further process, N-substituted compounds of Formula (I) may be prepared by treating the anion of an amide of Formula (XII):



wherein R<sub>1</sub> and R<sub>2</sub> with:

(a) a nitrile of the Formula (XIII):

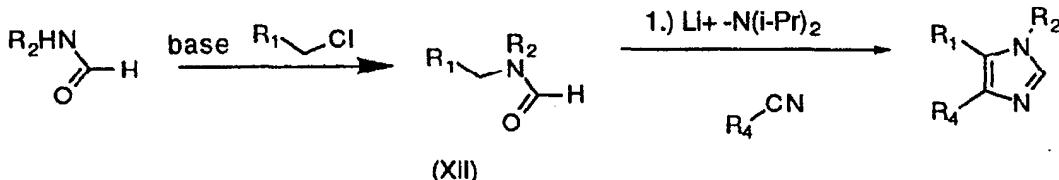


wherein R<sub>4</sub> is as hereinbefore defined, or

(b) an excess of an acyl halide, for instance an acyl chloride, of the Formula (XIV):



10 15 wherein R<sub>4</sub> is as hereinbefore defined and Hal is halogen, or a corresponding anhydride, to give a *bis*-acylated intermediate which is then treated with a source of ammonia, such as ammonium acetate.



20

SCHEME V

One variation of this approach is illustrated in Scheme V above. A primary amine (R<sub>2</sub>NH<sub>2</sub>) is treated with a halomethyl heterocycle of Formula R<sub>1</sub>CH<sub>2</sub>X to give the secondary amine which is then converted to the amide by standard techniques.

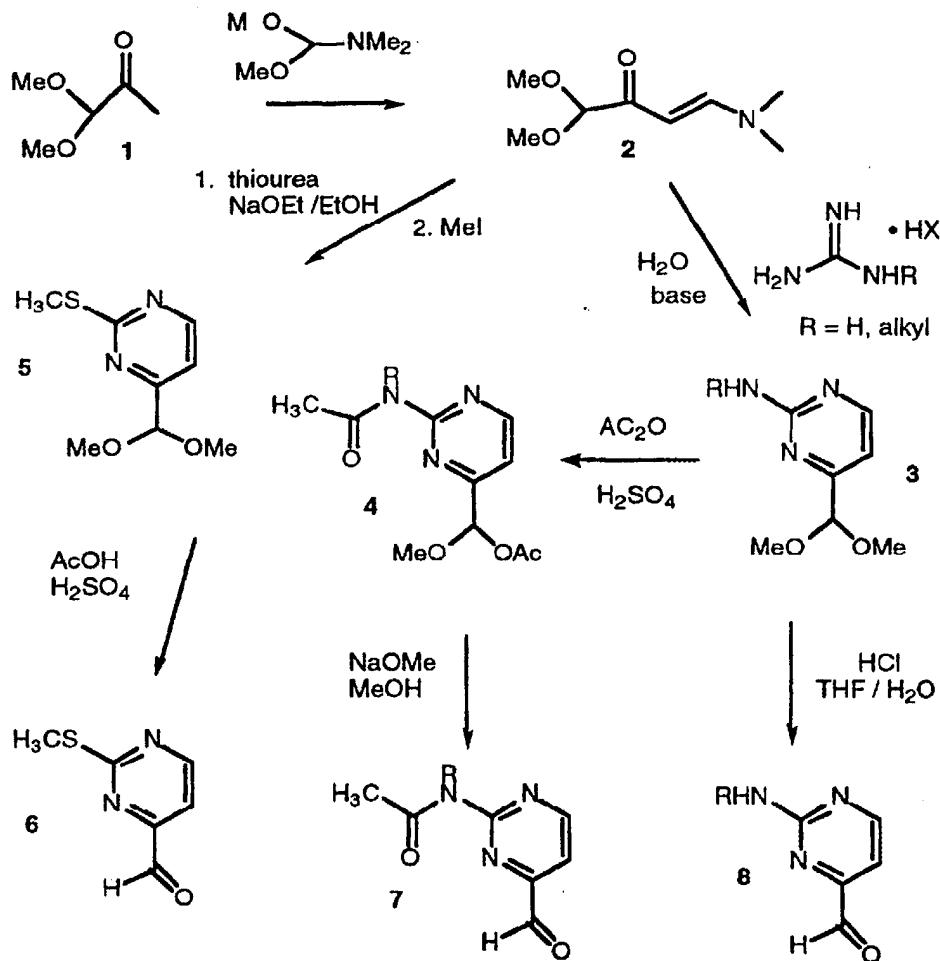
25 Alternatively the amide may be prepared as illustrated in scheme V by alkylation of the formamide with R<sub>1</sub>CH<sub>2</sub>X. Deprotonation of this amide with a strong amide base, such as lithium di-*iso*-propyl amide or sodium *bis*-(trimethylsilyl)amide, followed by

addition of an excess of an aroyl chloride yields the *bis*-acylated compound which is then closed to an imidazole compound of Formula (I), by heating in acetic acid containing ammonium acetate. Alternatively, the anion of the amide may be reacted with a substituted aryl nitrile to produce the imidazole of Formula (I) directly.

5

The following description and schemes are further exemplification of the process as previously described above in Scheme I. Various pyrimidine aldehyde derivatives 6, 7 and 8 as depicted in scheme VI below, can be prepared by modification of the procedures of Bredereck et al. (*Chem. Ber.* 1964, 97, 3407) whose disclosure is incorporated by reference herein. These pyrimidine aldehydes are then utilized as intermediates in the synthesis as further described herein. The unprotected amino aldehyde derivative, e.g. 8, can be somewhat unstable. Use of an acetolysis procedure, as described in Scheme VI, wherein the aldehyde 7 is isolated as the acetamide derivative, (compound 3 is converted to 7, via the intermediate 4) and leads to a more stable compound for use in the 10 cycloaddition reaction to make compounds of Formula (I).

15 General acetolysis conditions, for such a reaction are employed and are well known to those of skill in the art. Suitable conditions are exemplified, for instance in Example 83. In greater detail, the reaction employs heating the 2-amino pyrimidine dialkoxy acetal with acetic anhydride in the presence of a catalytic amount of 20 concentrated sulfuric acid, which simultaneously acetylates the amine and leads to the exchange of one of the alkoxy groups for an acetoxy group. The resultant compound is converted to the aldehyde by deacetylation with a catalytic amount of an alkoxide salt and the corresponding alcohol solvent, e.g. Na<sup>+</sup> methoxide and methanol. Alternatively, higher yields can be obtained by first acetylating the amine with acetic anhydride and 25 then affecting exchange by subsequent addition of concentrated sulfuric acid.



SCHEME VI

The reaction of imines with tosylmethyl isonitriles was first reported by van Leusen (van Leusen, et al., *J. Org. Chem.* 1977, 42, 1153.) Reported were the following 5 conditions: tert butyl amine(*t*BuNH<sub>2</sub>) in dimethoxyethane (DME), K<sub>2</sub>CO<sub>3</sub> in MeOH, and NaH in DME. Upon re-examination of these conditions each was found to produce low yields. A second pathway involving amine exchange to produce the *t*-butyl imine followed by reaction with the isocyanide to produce a 1-*t*Bu imidazole was also operating. This will likely occur using any primary amine as a base. The secondary 10 amines, while not preferred may be used, but may also decompose the isonitrile slowly. Reactions will likely require about 3 equivalents of amine to go to completion, resulting in approximately 50% isolated yields. Hindered secondary amines (diisopropylamine) while usable are very slow and generally not too effective. Use of tertiary and aromatic amines, such as pyridine, and triethylamine gave no reaction under certain test 15 conditions, but more basic types such as DBU, and 4-dimethylamino pyridine (DMAP) while slow, did produce some yields and hence may be suitable for use herein.

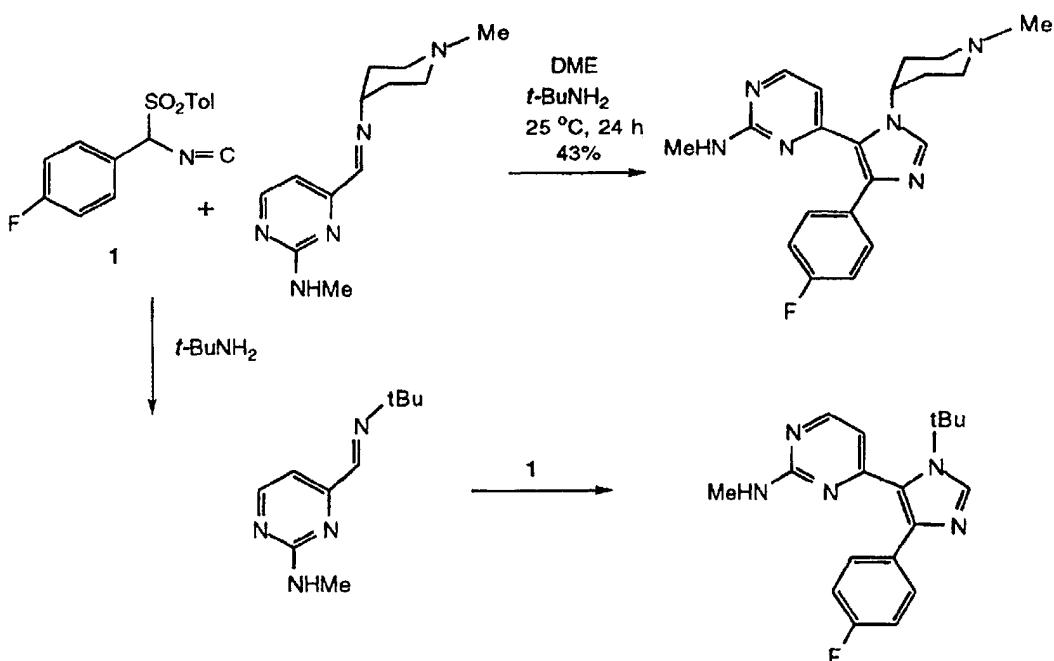
As depicted in Schemes VII and VIII below, the pyrimidine aldehydes of Scheme VI, can be condensed with a primary amine, to generate an imine, which may suitably be isolated or reacted in situ, with the desired isonitrile in the presence of a variety of suitable bases, and solvents as described herein to afford the 5-(4-pyrimidinyl)-imidazoles, wherein R<sub>2</sub> and R<sub>4</sub> are as defined herein for Formula (I) compounds.

One preferred method for preparing compounds of Formula (I) is shown below in Scheme VII. The imines, prepared and isolated in a separate step where often tars, which were hard to handle. The black color was also often carried over into the final product. The yields, for making the imines varied, and environmentally less-acceptable solvents, such as CH<sub>2</sub>Cl<sub>2</sub> were often used in their preparation.

This reaction, wherein p=2 requires a suitable base for the reaction to proceed. The reaction requires a base strong enough to deprotonate the isonitrile. Suitable bases include an amine, a carbonate, a hydride, or an alkyl or aryl lithium reagent; or mixtures thereof. Bases include, but are not limited to, potassium carbonate, sodium carbonate, primary and secondary amines, such as t-butylamine, diisopropyl amine, morpholine, piperidine, pyrrolidine, and other non-nucleophilic bases, such as DBU, DMAP and 1,4-diazabicyclo[2.2.2]octane (DABCO).

Suitable solvents for use herein, include but are not limited to N,N-dimethyl-formamide (DMF), MeCN, halogenated solvents, such as methylene chloride or chloroform, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), alcohols, such as methanol or ethanol, benzene, toluene, DME or EtOAc.. Preferably the solvent is DMF, DME, THF, or MeCN, more preferably DMF. Product isolation may generally be accomplished by adding water and filtering the product as a clean compound. The mixture is non-nucleophilic, thus no isonitrile decomposition occurs.

- 25 -

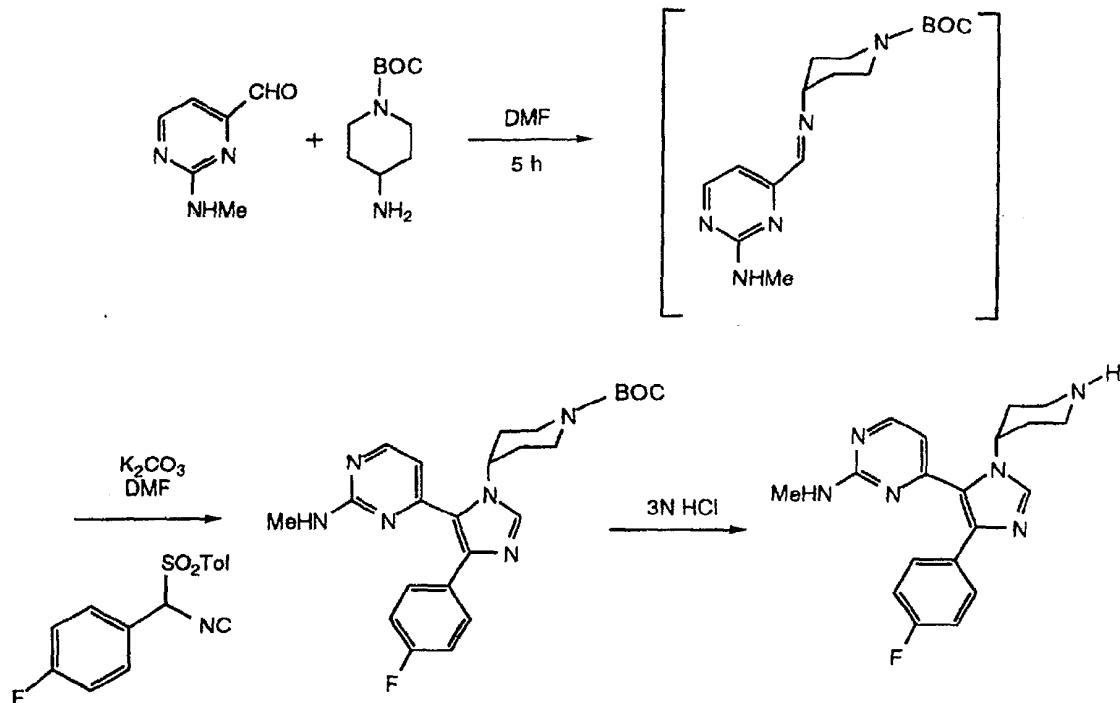
SCHEME VII

While not convenient for large scale work, addition of NaH, instead of t-butylamine, to the isonitrile, perhaps with temperatures lower than 25 °C (in THF) are likely needed. Additionally, BuLi has also been reported to be an effective base for deprotonating tosyl benzylisonitriles at -50 °C. (DiSanto, R.; Costi, R.; Massa, S.; Artico, M. *Synth. Commun.* 1995, 25, 795).

Various temperature conditions may be utilized depending upon the preferred base. For instance, tBuNH<sub>2</sub>/DME, K<sub>2</sub>CO<sub>3</sub>/MeOH, K<sub>2</sub>CO<sub>3</sub> in DMF, at temperatures above 40 °C, the yields may drop to about 20% but little difference is expected between 0 °C and 25 °C. Consequently, temperature ranges below 0 °C, and above 80 °C are contemplated as also being within the scope of this invention. Preferably, the temperature ranges are from about 0 °C to about 25 °C. For purposes herein, room temperature, which is depicted as 25 °C, but it is recognized that this may vary from 20 °C to 30 °C.

As shown in Scheme VIII below, the imine is preferably formed in situ in a solvent. This preferred synthesis, is a process which occurs as a one-pot synthesis. Suitably, when the primary amine is utilized as a salt, such as in the dihydrochloride salt in the Examples, the reaction may further include a base, such as potassium carbonate prior to the addition of the isonitrile. Alternatively, the piperidine nitrogen may be required to be protected as shown below. Reaction conditions, such as solvents, bases, temperatures, etc. are similar to those illustrated and discussed above for the isolated imine as shown in Scheme VIII. One skilled in the art would readily

recognize that under some circumstances, the in situ formation of the imine may require dehydrating conditions, or may require acid catalysis.



SCHEME VIII

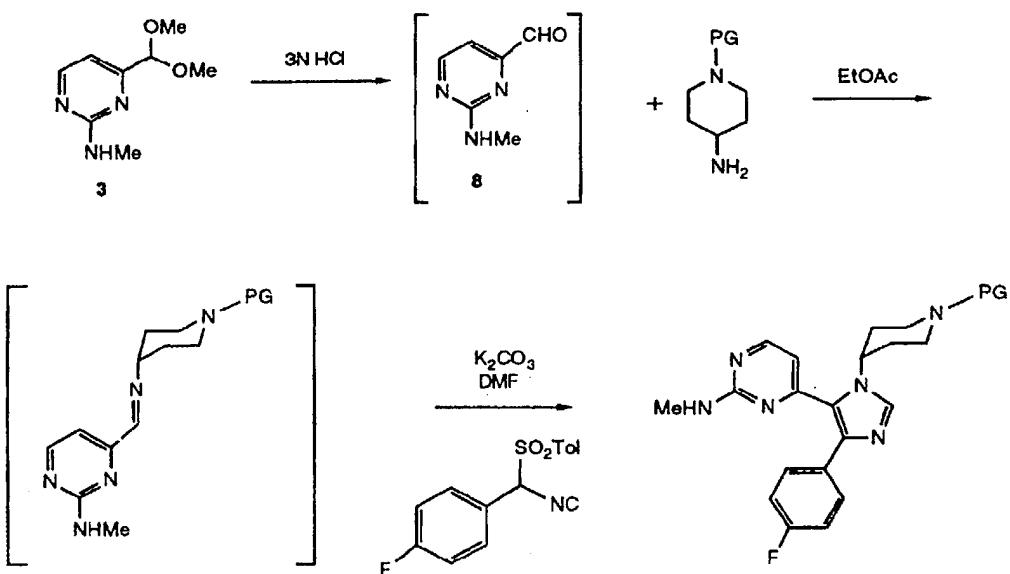
5

Another method for preparing compounds of Formula (I) is shown below in Scheme VIIIa. To avoid the difficulty associated with isolating the pyrimidine aldehyde 8, it is possible to hydrolyze the acetal 3 to aldehyde 8 as described herein. The aldehyde 8, formed in situ, can be treated sequentially with a primary amine, ethyl acetate, and NaHCO<sub>3</sub> to form the corresponding imine in situ, which is extracted into the ethyl acetate. Addition of the isonitrile, a carbonate base and DMF allows for the formation of the 5-(4-pyrimidinyl)-imidazoles, wherein R<sub>2</sub> and R<sub>4</sub> are as defined herein for Formula (I) compounds.

10

While it is recognized that Schemes VII, VIII, and VIII(a) are shown using a piperidine ring in the R<sub>2</sub> position this is for illustration purposes only and any suitable R<sub>2</sub> as defined herein may be utilized.

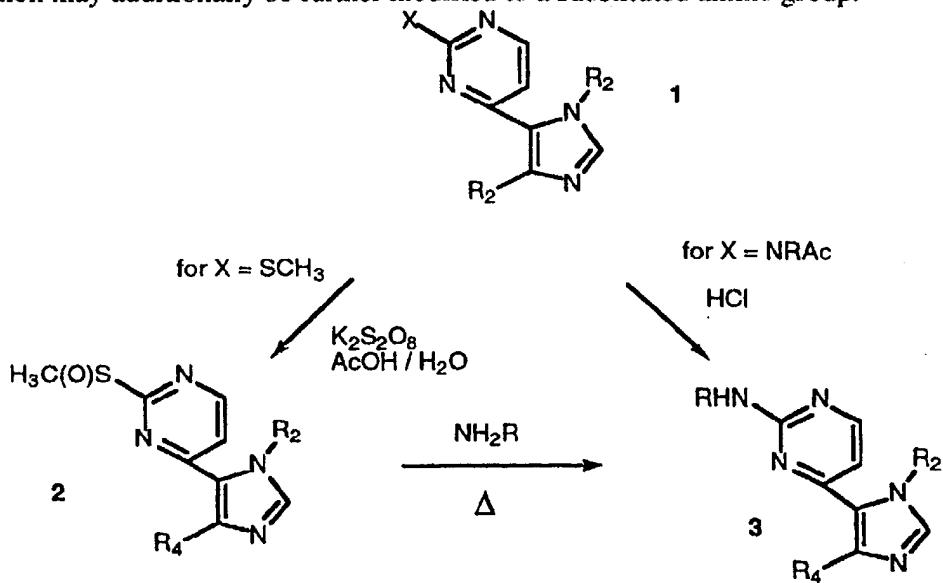
- 27 -



SCHEME VIIa

5 The preferred method of synthesis for compounds of Formula (I) also provides for a suitable and reliable method for introduction of an S(O)alkyl moiety on the pyrimidine (R<sub>1</sub> group) by using, for instance, the 2-methylthio pyrimidine aldehyde derivative, as is also described in the Examples section.

10 In scheme IX below (X=S Methyl), compound 1, while a final product may also be used as a precursor, as previously noted to make further compounds of formula (I). In this particular instance the methylthio moiety is oxidized to the methyl sulfinyl moiety which may additionally be further modified to a substituted amino group.

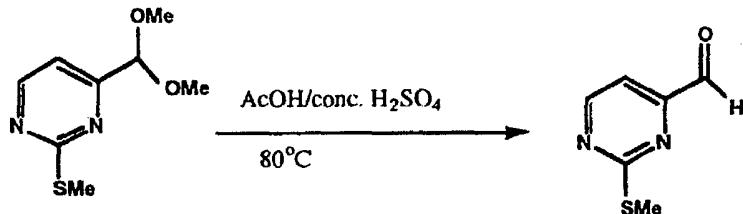


SCHEME IX

Another embodiment of the present invention is the novel hydrolysis of 2-thiomethylpyrimidine acetal to 2-thiomethylpyrimidine aldehyde, as shown in Scheme X below. Hydrolysis of the acetal to aldehyde using various known reaction conditions, such as formic acid, did not produce a satisfactory yield of the aldehyde, <13%) was obtained. The preferred synthesis involves the use of AcOH (fresh) as solvent and concentrated H<sub>2</sub>SO<sub>4</sub> under heating conditions, preferably a catalytic amount of sulfuric acid. Heating conditions include temperatures from about 60 to 85°C, preferably from about 70° to about 80°C as higher temperatures show a darkening of the reaction mixture.

10 After the reaction is completed the mixture is cooled to about room temperature and the acetic acid is removed. An alternative procedure to this involves heating the acetal in 3N HCl at 40°C for about 18 hours, cooling and extracting the bicarbonate neutralized solution into EtOAc.

15

SCHEME X

20 The final 2-aminopyrimidin-4-yl imidazole compounds of Formula (I), as well as similar pyridine containing compounds can be prepared by one of three methods: 1) direct reaction of the 2-aminopyrimidine imine with the isonitrile; 2) condensation of the 2-acetamidopyrimidine imine with the isonitrile followed by removal of the acetamido group and 3) oxidation of the 2-methylthiopyrimidine derivative to the corresponding sulfoxide followed by displacement with the desired amine.

25 While these schemes herein are presented, for instance, with an optionally substituted piperidine moiety for the resultant R<sub>2</sub> position, or a 4-fluoro phenyl for R<sub>4</sub>, any suitable R<sub>2</sub> moiety or R<sub>4</sub> moiety may be added in this manner if it can be prepared on the primary amine. Similarly, any suitable R<sub>4</sub> can be added via the isonitrile route.

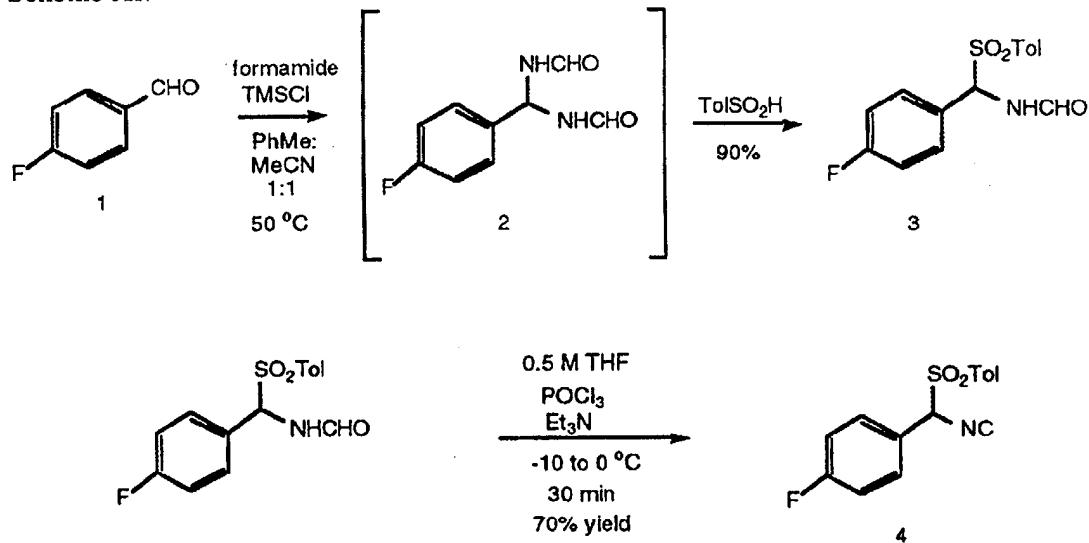
30 The compounds of Formula (II), in Scheme I, may be prepared by the methods of Van Leusen et al., supra. For example a compound of the Formula (II) may be prepared by dehydrating a compound of the Formula (IV)-Scheme I, wherein Ar, R<sub>4</sub> and p are as defined herein.

Suitable dehydrating agents include phosphorus oxychloride, oxalyl chloride, thionyl chloride, phosgene, or tosyl chloride in the presence of a suitable base such as triethylamine or diisopropylethylamine, or similar bases, etc. such as pyridine. Suitable solvents are dimethoxy ether, tetrahydrofuran, or halogenated solvents, preferably THF.

The reaction is most efficient when the reaction temperatures are kept between -10°C and 0°C. At lower temperatures incomplete reaction occurs and at higher temperatures, the solution turns dark and the product yield drops.

The compounds of formula (IV)-Scheme I may be prepared by reacting a compound of the formula (V)-Scheme I,  $R_4\text{CHO}$  where  $R_4$  is as defined herein, with  $\text{ArS(O)}_p\text{H}$  and formamide with or without water removal, preferably under dehydrating conditions, at ambient or elevated temperature e.g. 30° to 150°, conveniently at reflux, optionally in the presence of an acid catalyst. Alternatively trimethylsilylchloride can be used in place of the acid catalyst. Examples of acid catalysts include camphor-10-sulphonic acid, formic acid, p-toluenesulphonic acid, hydrogen chloride or sulphuric acid.

An optimal method of making an isonitrile of Formula (II) is illustrated below, in Scheme XI.



SCHEME XI

The conversion of the substituted aldehyde to the tosylbenzyl formamide may be accomplished by heating the aldehyde, 1-Scheme XI, with an acid, such as p-toluenesulfonic acid, formic acid or camphorsulfonic acid; with formamide and p-toluene-sulfinic acid [under reaction conditions of about 60°C for about 24 hours]. Preferably, no solvent is used. The reaction, may give poor yields (< 30%) when solvents, such as DMF, DMSO, toluene, acetonitrile, or excess formamide are used. Temperatures less than 60°C are generally poor at producing the desired product, and temperatures in excess of 60°C may produce a product which decomposes, or obtain a benzylic bis-formamide, 2-Scheme XI. In Example 23 (a), described in WO 95/02591, Adams et al., synthesizes 4-Fluorophenyl-tosylmethylformamide, a compound of Formula (IV)-Scheme I, wherein  $p = 2$ . This procedure differs from that presently described herein by the following conditions, using the sodium salt of toluene sulfinic acid, neat which

process results in uneven heating, lower yields and lower reproducibility than the present invention, as described herein which uses sulfinic acid and allows for use of non-aqueous conditions.

Conditions for making  $\alpha$ -(p-Toluenesulfonyl)-4-fluorobenzylisonitrileas

5 described in Example 23 (b), of WO 95/02591, Adams et al., used as a solvent MeCl to extract the product and DME as solvent. The present invention improves upon this process by utilizing less expensive solvents, such as THF and EtOAc to extract. Further higher yields are obtained by recrystallizing with an alcohol, such as 1-propanol, although other alcohols, such as methanol, ethanol and butanols are acceptable. Previously, the  
10 compound was partially purified using chromatography techniques, and hazardous solvents for additional purifications.

Another embodiment of the present invention is the synthesis of the tosyl benzyl formamide compound, achieved by reacting the bisformamide intermediate, 2-Scheme  
15 XI. with p-toluenesulfinic acid. In this preferred route, preparation of the bis-formamide from the aldehyde is accomplished by heating the aldehyde with formamide, in a suitable solvent with acid catalysis. Suitable solvents are toluene, acetonitrile, DMF, and DMSO or mixtures thereof. Acid catalysts, are those well known in the art, and include but are not limited to hydrogen chloride, p-toluenesulfonic acid, camphorsulfonic acid, and other  
20 anhydrous acids. The reaction can be conducted at temperatures ranging from about 25°C to 110°C, preferably about 50°C, suitably for about 4 to about 5 hours, longer reaction times are also acceptable. Product decomposition and lower yields may be observed at higher temperatures (>70°C) at prolonged reaction times. Complete conversion of the product generally requires water removal from the reaction mixture.

25 Preferred conditions for converting a bis-formamide derivative to the tosyl benzyl formamide are accomplished by heating the bisformamide in a suitable solvent with an acid catalyst and p-toluenesulfinic acid. Solvents for use in this reaction include but are not limited to toluene, and acetonitrile or mixtures thereof. Additional mixtures of these solvents with DMF, or DMSO may also be used but may result in  
30 lower yields. Temperatures may range from about 30°C to about 100°C. Temperatures lower than 40°C and higher than 60°C are not preferred as the yield and rate decreases. Preferably the range is from about 40 to 60°C, most preferably about 50°C. The optimal time is about 4 to 5 hours, although it may be longer. Preferably, acids used include but are not limited to, toluenesulfonic acid, camphorsulfonic acid, and  
35 hydrogen chloride and other anhydrous acids. Most preferably the bisformamide is heated in toluene:acetonitrile in a 1:1 ratio, with p-toluenesulfinic acid and hydrogen chloride.

Another embodiment of the present invention is the preferred synthetic route for synthesis of the tosylbenzyl formamide compound which is accomplished using a one-pot procedure. This process first converts the aldehyde to the bis-formamide derivative and subsequently reacts the bis-formamide derivative with toluenesulfinic acid. This 5 procedure combines the optimized conditions into a single, efficient process. High yields, >90% of the aryl benzylformamide may be obtained in such a manner.

Preferred reaction conditions employ a catalyst, such as trimethylsilyl chloride (TMSCl), in a preferred solvent, toluene:acetonitrile, preferably in a 1:1 ratio. A reagent, such as TMSCl, is preferred which reacts with water produced therein and at the same 10 time produces hydrogen chloride to catalyze the reaction. Also preferred is use of hydrogen chloride and p-toluenesulfonic acid. Therefore, three suitable reaction conditions for use herein include 1) use of a dehydrating agent which also provides hydrogen chloride, such as TMSCl; or by 2) use of a suitable dehydrating agent and a suitable source of acid source, such as but not limited to, camphorsulfonic acid, hydrogen 15 chloride or toluenesulfonic acid; and 3) alternative dehydrating conditions, such as the azeotropic removal of water, and using an acid catalyst and p-toluene sulfinic acid.

Compounds of the formula (II) where p is 2 may also be prepared by reacting in 20 the presence of a strong base a compound of the formula (VI) -Scheme I,  $R_4CH_2NC$  with a compound of the formula (VII)-Scheme I,  $ArSO_2L_1$  wherein  $R_4$  and  $Ar$  are as defined herein and  $L_1$  is a leaving group such as halo, e.g. fluoro. Suitable strong bases include, but are not limited to, alkyl lithiums such as butyl lithium or lithium diisopropylamide (van Leusen et al., *Tetrahedron Letters*, No. 23, 2367-68 (1972)).

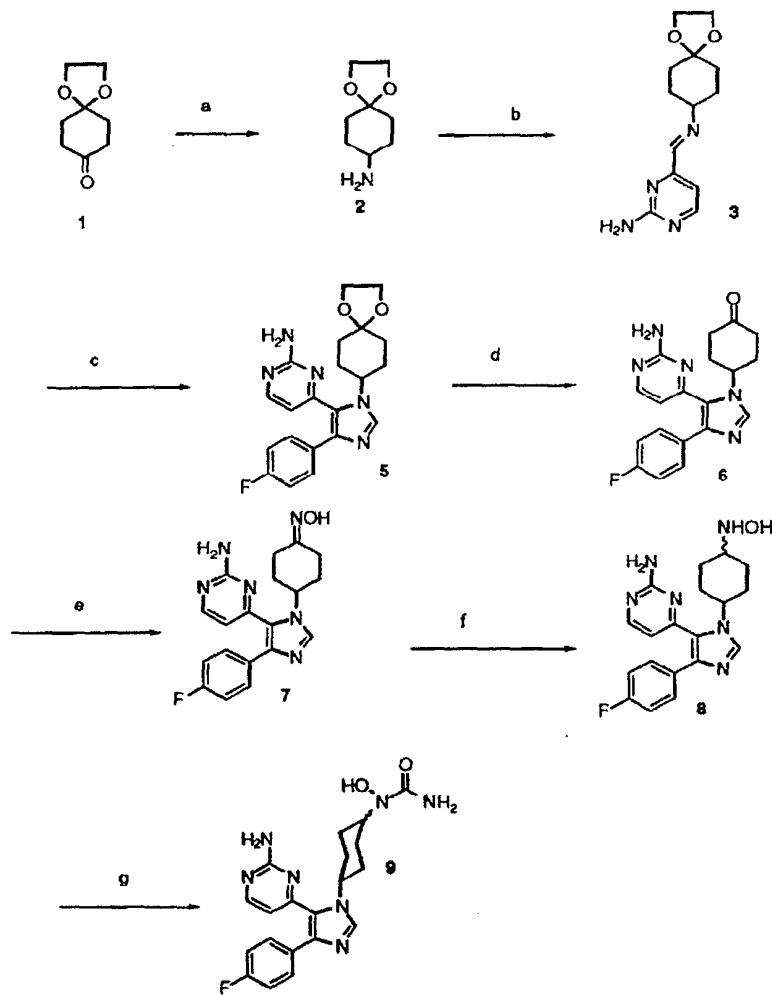
The compounds of formula (VI)-Scheme I may be prepared by reacting a 25 compound of the formula (VIII)-Scheme I,  $R_4CH_2NH_2$  with an alkyl formate (e.g. ethylformate) to yield an intermediate amide which can be converted to the desired isonitrile by reacting with well known dehydrating agent, such as but not limited to oxalyl chloride, phosphorus oxychloride or tosyl chloride in the presence of a suitable base such as triethylamine.

Alternatively a compound of the formula (VIII) - Scheme I may be converted to 30 a compound of the formula (VI)- Scheme I by reaction with chloroform and sodium hydroxide in aqueous dichloromethane under phase transfer catalysis.

The compounds of the formula (III) - Scheme I may be prepared by reacting a compound of the formula  $R_1CHO$  with a primary amine  $R_2NH_2$ .

The amino compounds of the formula (VIII) - Scheme I are known or can be 35 prepared from the corresponding alcohols, oximes or amides using standard functional group interconversions.

In Scheme XII below, the compound 5-Scheme 12 is shown in the Examples section as Example 2, the compound 6-Scheme 12 as Example 4; compound 7-Scheme 12 as Example 5; 8-Scheme 12 as Example 6; and compound 9-Scheme 12 as Example 7.

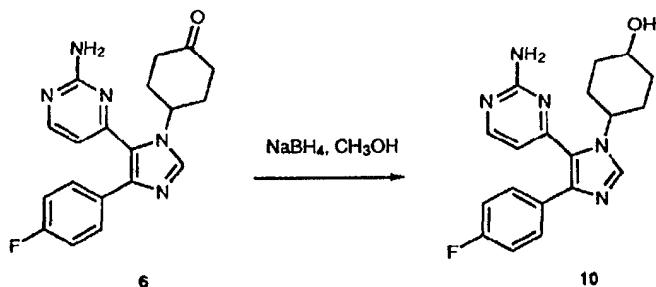


5 Conditions: a) i.  $\text{NH}_2\text{OH}\cdot\text{HCl}$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$ ; ii. Raney Ni,  $\text{H}_2$ ; b) 2-aminopyrimidinyl-4-carboxaldehyde,  $\text{CH}_2\text{Cl}_2$ ; c) 4-fluorophenyl-tolylthiomethylisocyanide, TBD,  $\text{CH}_2\text{Cl}_2$ ; d) i.  $\text{HCl}$ ,  $\text{H}_2\text{O}$ ; ii.  $\text{Na}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$ ; e)  $\text{NH}_2\text{OH}\cdot\text{HCl}$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$ ; f.  $\text{NaCNBH}_3$ ,  $\text{MeOH}$ ; g)  $\text{KNCO}$ ,  $\text{DMF}$ ,  $\text{H}_2\text{O}$ ,  $\text{HOAc}$ .

### SCHEME XII

10 Cycloalkanones such as 1-Scheme XII (available from Aldrich Chemical Co., Milwaukee, Wi) may be converted to cycloalkylamines such as 2-Scheme XII by conventional procedures for reductive amination such as oxime formation with hydroxylamine in  $\text{H}_2\text{O}$  followed by reduction of the oxime to the amine by standard conditions such as catalytic hydrogenation with Raney Ni in an  $\text{H}_2$  atmosphere. The

resulting cycloalkylamines such as 2-Scheme XII may be reacted with aryl aldehydes such as 2-aminopyrimidinyl-4-carboxaldehyde in non-hydroxylic organic solvents to form imines such as 3-Scheme XII. Depending on the degree of activation of the aldehydes towards imine formation, catalytic acid (such as toluenesulfonic acid) and dehydrating conditions (such as azeotropic removal of water in refluxing benzene) may or may not be needed. Imines such as 3-Scheme XII may be converted to 1,4 diaryl imidazoles alkylated with cycloalkyl groups by reaction with isonitriles such as 4-fluorophenyl-tolylthiomethylisocyanide in the presence of a base such as 1,5,7-triazabicyclo[4.4.0]-dec-5-ene (TBD) in organic solvents such as  $\text{CH}_2\text{Cl}_2$ . In this way 3-Scheme XII was converted to 5-Scheme XII. Cycloalkyl ketal substituted imidazoles such as 5-Scheme XII are hydrolyzed with aqueous acids (such as aqueous HCl) followed by neutralization with base (such as aqueous  $\text{Na}_2\text{CO}_3$ ) to afford ketones such as 6-Scheme VI. 6-Scheme XII is converted to the oxime 7-Scheme XII with hydroxylamine in  $\text{H}_2\text{O}$ . 7-Scheme XII is converted to the hydroxylamine 8-Scheme XII by reduction with sodium cyano borohydride in methanol. 8-Scheme X is converted to the hydroxyureas 9-Scheme XII by the procedure of Adams et al (WO 91/14674 published 3 October 1991).

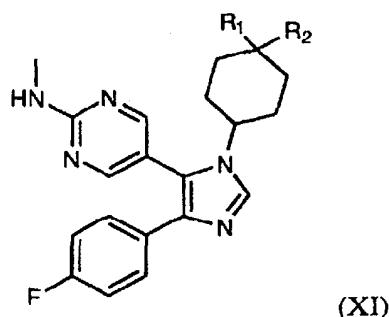


20

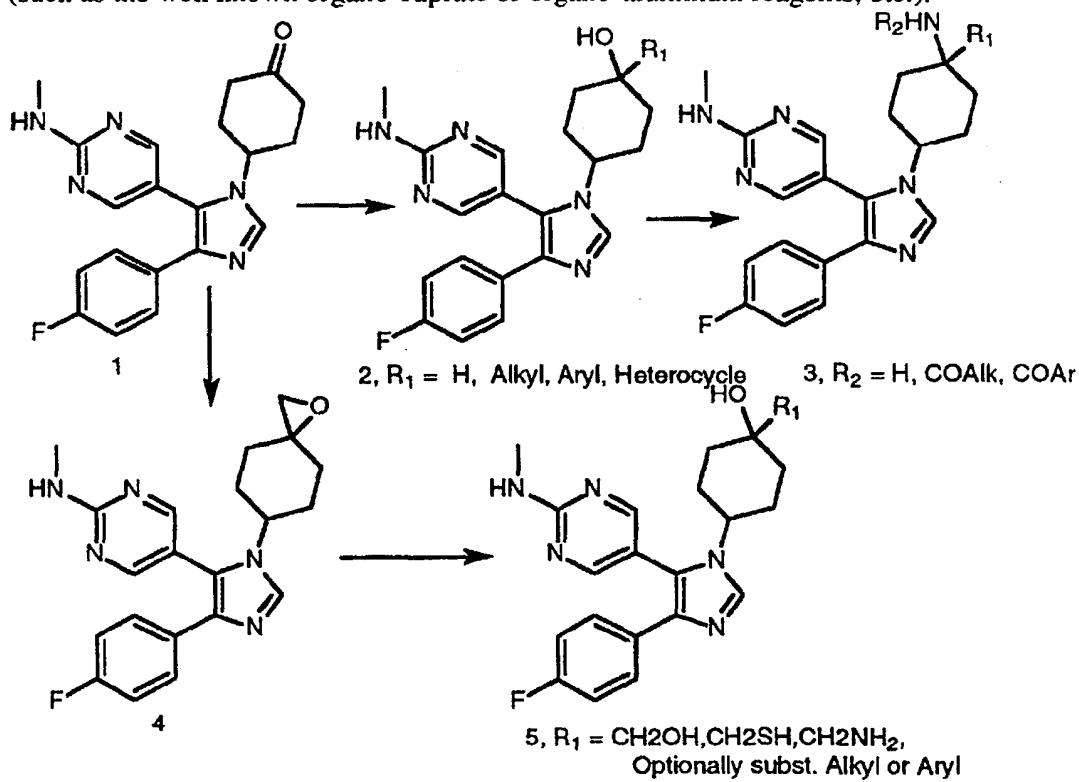
### SCHEME XIII

In the above noted Scheme, the alcohol 10-Scheme 13 may be prepared by reducing the ketone of 6-Scheme 13 with a suitable reducing agent, such as  $\text{NaBH}_4$ .

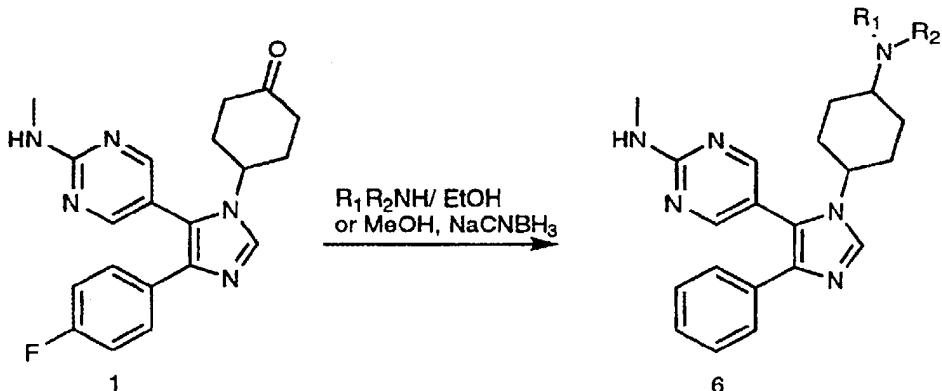
In formula XI below, R<sub>1</sub> is may be an optionally substituted alkyl, aryl or a heteroaryl group and R<sub>2</sub> is either an OH, NH<sub>2</sub> or SH, or R<sub>1</sub> and R<sub>2</sub> together can form a C<sub>3</sub>-7 cycloalkyl ring, such as, for example a pyrrolidine or piperidine ring. Some representative examples of such compounds are illustrated in scheme XIV below.

SCHEME XIV

The ketone 1 can be reacted with any organometallic reagent ( $R_1M$ ) to afford the corresponding alcohol 2 (wherein  $R_1$  can be hydrogen or any optionally substituted alkyl 5 aryl, arylalkyl, heterocyclic, heterocyclic alkyl, etc. moiety). The alcohol 2 can be converted to the neopentyl amine 3, by using the classical Ritter reaction well known by those of skill in the art. The amine 3 can be acylated or sulfonylated. The ketone 1 can be 10 can be transformed into an spirooxirane 4 by reagents such as dimethylsulfonium methylide and dimethyl sulfoxonium methylide. The oxirane 4 can be ring opened with a plethora of nucleophiles such as hydroxides, thiolates, amines, organometallic reagents (such as the well known organo-cuprate or organo-aluminum reagents, etc.).

SCHEME XIV

The ketone **1** -Scheme XV may also be subjected to reductive amination by any primary or secondary amines to afford amines **6**-Scheme XV.



$R_1$  and  $R_2$  can be any alkyl or aryl group,  $R_1$  and  $R_2$  can also be a part of a ring

### SCHEME XV

5

Suitable protecting groups for use with hydroxyl groups and the imidazole nitrogen are well known in the art and described in many references, for instance, Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981. Suitable examples of hydroxyl protecting groups include silyl ethers, such as t-butyldimethyl or t-butyldiphenyl, and alkyl ethers, such as methyl connected by an alkyl chain of variable link,  $(CR_{10}R_{20})_n$ . Suitable examples of imidazole nitrogen protecting groups include tetrahydropyranyl.

15 Pharmaceutically acid addition salts of compounds of Formula (I) may be obtained in known manner, for example by treatment thereof with an appropriate amount of acid in the presence of a suitable solvent.

## METHODS OF TREATMENT

The compounds of Formula (I) or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated cytokine production by such mammal's cell, such as but not limited to monocytes and/or macrophages.

Compounds of Formula (I) are capable of inhibiting proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF and are therefore of use in therapy. IL-1, IL-6, IL-8 and TNF affect a wide variety of cells and tissues and these cytokines, as well as other leukocyte-derived cytokines, are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these pro-inflammatory

cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

Compounds of Formula (I) are capable of inhibiting inducible proinflammatory proteins, such as COX-2, also referred to by many other names such as prostaglandin endoperoxide synthase-2 (PGHS-2) and are therefore of use in therapy. These proinflammatory lipid mediators of the cyclooxygenase (CO) pathway are produced by the inducible COX-2 enzyme. Regulation, therefore of COX-2 which is responsible for the these products derived from arachidonic acid, such as prostaglandins affect a wide variety of cells and tissues are important and critical inflammatory mediators of a wide variety of disease states and conditions. Expression of COX-1 is not effected by compounds of Formula (I). This selective inhibition of COX-2 may alleviate or spare ulcerogenic liability associated with inhibition of COX-1 thereby inhibiting prostaglandins essential for cytoprotective effects. Thus inhibition of these proinflammatory mediators is of benefit in controlling, reducing and alleviating many of these disease states. Most notably these inflammatory mediators, in particular prostaglandins, have been implicated in pain, such as in the sensitization of pain receptors, or edema. This aspect of pain management therefore includes treatment of neuromuscular pain, headache, cancer pain, and arthritis pain. Compounds of Formula (I) or a pharmaceutically acceptable salt thereof, are of use in the prophylaxis or therapy in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

Accordingly, the present invention provides a method of inhibiting the synthesis of COX-2 which comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The present invention also provides for a method of prophylaxis treatment in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering an effective cytokine-interfering amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

In particular, compounds of Formula (I) or a pharmaceutically acceptable salt thereof are of use in the prophylaxis or therapy of any disease state in a human, or other mammal, which is exacerbated by or caused by excessive or unregulated IL-1, IL-8 or TNF production by such mammal's cell, such as, but not limited to, monocytes and/or macrophages.

Accordingly, in another aspect, this invention relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, stroke, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by

5 endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, multiple sclerosis, cachexia, bone resorption, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes, pancreatic  $\beta$  cells and Alzheimer's disease.

10 In a further aspect, this invention relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

15 Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, such as osteoporosis,

20 reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

25 Compounds of Formula (I) are also useful in the treatment of viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibiting-compounds of Formula (I).

30 Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as but not limited to, Herpes Zoster and Herpes Simplex. Accordingly, in a further aspect, this invention relates to a method of treating a mammal afflicted with a human immunodeficiency virus (HIV) which comprises administering to such mammal an effective TNF

35 inhibiting amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than in humans, in need of inhibition of TNF production.

TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to, lentivirus infections such as, equine infectious anaemia virus, caprine arthritis virus, visna virus, or maedi virus or 5 retrovirus infections, such as but not limited to feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus or other retroviral infections.

The compounds of Formula (I) may also be used topically in the treatment or prophylaxis of topical disease states mediated by or exacerbated by excessive cytokine 10 production, such as by IL-1 or TNF respectively, such as inflamed joints, eczema, psoriasis and other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

Compounds of Formula (I) have also been shown to inhibit the production of IL-15 8 (Interleukin-8, NAP). Accordingly, in a further aspect, this invention relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated IL-8 production 20 is implicated in exacerbating and/or causing the disease. These diseases are characterized by massive neutrophil infiltration such as, psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. All of these diseases are associated with increased IL-8 production which is responsible for the chemotaxis of neutrophils into 25 the inflammatory site. In contrast to other inflammatory cytokines (IL-1, TNF, and IL-6), IL-8 has the unique property of promoting neutrophil chemotaxis and activation. Therefore, the inhibition of IL-8 production would lead to a direct reduction in the neutrophil infiltration.

The compounds of Formula (I) are administered in an amount sufficient to 30 inhibit cytokine, in particular IL-1, IL-6, IL-8 or TNF, production such that it is regulated down to normal levels, or in some case to subnormal levels, so as to ameliorate or prevent the disease state. Abnormal levels of IL-1, IL-6, IL-8 or TNF, for instance in the context of the present invention, constitute: (i) levels of free (not cell bound) IL-1, IL-6, IL-8 or TNF greater than or equal to 1 picogram per ml; (ii) any cell 35 associated IL-1, IL-6, IL-8 or TNF; or (iii) the presence of IL-1, IL-6, IL-8 or TNF mRNA above basal levels in cells or tissues in which IL-1, IL-6, IL-8 or TNF, respectively, is produced.

The discovery that the compounds of Formula (I) are inhibitors of cytokines, specifically IL-1, IL-6, IL-8 and TNF is based upon the effects of the compounds of Formulas (I) on the production of the IL-1, IL-8 and TNF in *in vitro* assays which are described herein.

5 As used herein, the term "inhibiting the production of IL-1 (IL-6, IL-8 or TNF)" refers to:

a) a decrease of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels by inhibition of the *in vivo* release of the cytokine by all cells, including but not limited to monocytes or macrophages;

10 b) a down regulation, at the genomic level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels;

c) a down regulation, by inhibition of the direct synthesis of the cytokine (IL-1, IL-6, IL-8 or TNF) as a posttranslational event; or

15 d) a down regulation, at the translational level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels.

As used herein, the term "TNF mediated disease or disease state" refers to any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF.

25 As used herein, the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however 30 also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) 35 and Tumor Necrosis Factor beta (TNF- $\beta$ ).

As used herein, the term "cytokine interfering" or "cytokine suppressive amount" refers to an effective amount of a compound of Formula (I) which will cause a decrease in the *in vivo* levels of the cytokine to normal or sub-normal levels, when given

to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production.

As used herein, the cytokine referred to in the phrase "inhibition of a cytokine, for use in the treatment of a HIV-infected human" is a cytokine which is implicated in 5 (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration.

As TNF- $\beta$  (also known as lymphotoxin) has close structural homology with TNF- $\alpha$  (also known as cachectin) and since each induces similar biologic responses and 10 binds to the same cellular receptor, both TNF- $\alpha$  and TNF- $\beta$  are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

A new member of the MAP kinase family, alternatively termed CSBP, p38, or RK, has been identified independently by several laboratories recently. Activation of 15 this novel protein kinase via dual phosphorylation has been observed in different cell systems upon stimulation by a wide spectrum of stimuli, such as physicochemical stress and treatment with lipopolysaccharide or proinflammatory cytokines such as interleukin-1 and tumor necrosis factor. The cytokine biosynthesis inhibitors, of the present invention, compounds of Formula (I), have been determined to be potent and selective 20 inhibitors of CSBP/p38/RK kinase activity. These inhibitors are of aid in determining the signaling pathways involvement in inflammatory responses. In particular, for the first time a definitive signal transduction pathway can be prescribed to the action of lipopolysaccharide in cytokine production in macrophages.

The cytokine inhibitors were subsequently tested in a number of animal models 25 for anti-inflammatory activity. Model systems were chosen that were relatively insensitive to cyclooxygenase inhibitors in order to reveal the unique activities of cytokine suppressive agents. The inhibitors exhibited significant activity in many such in vivo studies. Most notable are its effectiveness in the collagen-induced arthritis model and inhibition of TNF production in the endotoxic shock model. In the latter 30 study, the reduction in plasma level of TNF correlated with survival and protection from endotoxic shock related mortality. Also of great importance are the compounds effectiveness in inhibiting bone resorption in a rat fetal long bone organ culture system. Griswold et al., (1988) *Arthritis Rheum.* **31**:1406-1412; Badger, et al., (1989) *Circ. Shock* **27**, 51-61; Votta et al., (1994) *in vitro. Bone* **15**, 533-538; Lee et al., (1993). B 35 *Ann. N. Y. Acad. Sci.* **696**, 149-170.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also

relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent.

Compounds of Formula (I), pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by 5 any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of Formula (I) may be administered in conventional dosage forms prepared by combining a compound of Formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of Formula (I) may also be administered in conventional dosages in 10 combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other 15 well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the Formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, 20 pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid 25 carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

30 Compounds of Formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of Formula (I) externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

35 Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to

the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the Formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the Formulation.

5        Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a  
10      moisturizer such as glycerol or an oil such as castor oil or arachis oil.

15      Creams, ointments or pastes according to the present invention are semi-solid Formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The Formulation may incorporate any suitable surface active agent such as  
20      an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

25      Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100° C. for half an hour.  
30      Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

35      Compounds of formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such

administration may be prepared by conventional techniques. Compounds of Formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol Formulation or a metered dose inhaler, may be prepared by conventional techniques.

5 For all methods of use disclosed herein for the compounds of Formula (I), the daily oral dosage regimen will preferably be from about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to 30 mg/kg, more preferably from about 0.5 mg to 15mg. The daily parenteral dosage regimen about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to about 30 mg/kg, and more preferably from 10 about 0.5 mg to 15mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable salt 15 thereof given per day for a defined number of days, can be ascertained by those skilled 20 in the art using conventional course of treatment determination tests.

The invention will now be described by reference to the following biological examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

25

#### BIOLOGICAL EXAMPLES

The cytokine-inhibiting effects of compounds of the present invention were determined by the following *in vitro* assays:

##### **Interleukin - 1 (IL-1)**

30 Human peripheral blood monocytes are isolated and purified from either fresh blood preparations from volunteer donors, or from blood bank buffy coats, according to the procedure of Colotta *et al*, J Immunol, 132, 936 (1984). These monocytes ( $1 \times 10^6$ ) are plated in 24-well plates at a concentration of 1-2 million/ml per well. The cells are allowed to adhere for 2 hours, after which time non-adherent cells are removed by 35 gentle washing. Test compounds are then added to the cells for about 1 hour before the addition of lipopolysaccharide (50 ng/ml), and the cultures are incubated at 37°C for an additional 24 hours. At the end of this period, culture super-natants are removed and clarified of cells and all debris. Culture supernatants are then immediately assayed for

IL-1 biological activity, either by the method of Simon *et al.*, *J. Immunol. Methods*, **84**, 85, (1985) (based on ability of IL-1 to stimulate a Interleukin 2 producing cell line (EL-4) to secrete IL-2, in concert with A23187 ionophore) or the method of Lee *et al.*, *J. ImmunoTherapy*, **6** (1), 1-12 (1990) (ELISA assay).

5

**Tumour Necrosis Factor (TNF):**

Human peripheral blood monocytes are isolated and purified from either blood bank buffy coats or plateletpheresis residues, according to the procedure of Colotta, R. *et al.*, *J Immunol*, **132**(2), 936 (1984). The monocytes are plated at a density of  $1 \times 10^6$  cells/ml medium/well in 24-well multi-dishes. The cells are allowed to adhere for 1 hour after which time the supernatant is aspirated and fresh medium (1ml, RPMI-1640, Whitaker Biomedical Products, Whitaker, CA) containing 1% fetal calf serum plus penicillin and streptomycin (10 units/ml) added. The cells are incubated for 45 minutes in the presence or absence of a test compound at 1nM-10mM dose ranges (compounds are solubilized in dimethyl sulfoxide/ethanol, such that the final solvent concentration in the culture medium is 0.5% dimethyl sulfoxide/0.5% ethanol). Bacterial lipopolysaccharide (*E. coli* 055:B5 [LPS] from Sigma Chemicals Co.) is then added (100 ng/ml in 10 ml phosphate buffered saline) and cultures incubated for 16-18 hours at 37°C in a 5% CO<sub>2</sub> incubator. At the end of the incubation period, culture supernatants are removed from the cells, centrifuged at 3000 rpm to remove cell debris. The supernatant is then assayed for TNF activity using either a radio-immuno or an ELISA assay, as described in WO 92/10190 and by Becker *et al.*, *J Immunol*, **147**, 4307.

IL-1 and TNF inhibitory activity does not seem to correlate with the property of the compounds of Formula (I) in mediating arachidonic acid metabolism inhibition. Further the ability to inhibit production of prostaglandin and/or leukotriene synthesis, by nonsteroidal anti-inflammatory drugs with potent cyclooxygenase and/or lipoxygenase inhibitory activity does not mean that the compound will necessarily also inhibit TNF or IL-1 production, at non-toxic doses.

30

**Interleukin -8 (IL-8) :**

Primary human umbilical cord endothelial cells (HUVEC) (Cell Systems, Kirland, Wa) are maintained in culture medium supplemented with 15% fetal bovine serum and 1% CS-HBGF consisting of aFGF and heparin. The cells are then diluted 20-fold before being plated (250 $\mu$ l) into gelating coated 96-well plates. Prior to use, culture medium are replaced with fresh medium (200 $\mu$ l). Buffer or test compound (25 $\mu$ l, at concentrations between 1 and 10 $\mu$ M) is then added to each well in quadruplicate wells and the plates incubated for 6h in a humidified incubator at 37°C in

an atmosphere of 5% CO<sub>2</sub>. At the end of the incubation period, supernatant is removed and assayed for IL-8 concentration using an IL-8 ELISA kit obtained from R&D Systems (Minneapolis, MN). All data is presented as mean value (ng/ml) of multiple samples based on the standard curve. IC<sub>50</sub>'s where appropriate are generated by non-linear regression analysis.

#### **Cytokine Specific Binding Protein Assay**

A radiocompetitive binding assay was developed to provide a highly reproducible primary screen for structure-activity studies. This assay provides many advantages over the conventional bioassays which utilize freshly isolated human monocytes as a source of cytokines and ELISA assays to quantify them. Besides being a much more facile assay, the binding assay has been extensively validated to highly correlate with the results of the bioassay. A specific and reproducible cytokine inhibitor binding assay was developed using soluble cytosolic fraction from THP.1 cells and a radiolabeled compound. Patent Application USSN 08/123175 Lee et al., filed September 1993, USSN: Lee et al., PCT 94/10529 filed 16 September 1994 and Lee et al., *Nature* 300, n(72), 739-746 (Dec. 1994) whose disclosures are incorporated by reference herein in its entirety describes the above noted method for screening drugs to identify compounds which interact with and bind to the cytokine specific binding protein (hereinafter CSBP). However, for purposes herein the binding protein may be in isolated form in solution, or in immobilized form, or may be genetically engineered to be expressed on the surface of recombinant host cells such as in phage display system or as fusion proteins. Alternatively, whole cells or cytosolic fractions comprising the CSBP may be employed in the screening protocol. Regardless of the form of the binding protein, a plurality of compounds are contacted with the binding protein under conditions sufficient to form a compound/ binding protein complex and compound capable of forming, enhancing or interfering with said complexes are detected.

Representative final compounds of Formula (I), of Formula (I), Examples 4, 7, 8, 10 to 21 have all demonstrated positive inhibitory activity in this binding assay.

30

#### **Prostaglandin endoperoxide synthase-2 (PGHS-2) assay:**

The following assay describes a method for determining the inhibitory effects of compounds of Formula (I) on human PGHS-2 protein expression in LPS stimulated human monocytes

35

#### **Method:**

Human peripheral blood monocytes were isolated from buffy coats by centrifugation through Ficoll and Percoll gradients. Cells were seeded at 2 X 10<sup>6</sup>/well in 24 well plates and allowed to adhere for 1 hour in RPMI supplemented with 1% human AB serum,

20mM L-glutamine, Penicillin-Streptomycin and 10mM HEPES. Compounds were added at various concentrations and incubated at 37°C for 10 minutes. LPS was added at 50 ng/well (to induce enzyme expression) and incubated overnight at 37°C. The supernatant was removed and cells washed once in cold PBS. The cells were lysed in 5 100µl of cold lysis buffer(50mM Tris/HCl pH 7.5, 150mM NaCl, 1% NP40, 0.5% sodium deoxycholate, 0.1% SDS, 300ug/ml DNase, 0.1% TRITON X-100, 1mM PMSF, 1mM leupeptin, 1mM pepstatin). The lysate was centrifuged (10,000 X g for 10 min. at 4°C) to remove debris and the soluble fraction was subjected to SDS PAGE. analysis 10 (12% gel). Protein separated on the gel were transferred onto nitrocellulose membrane by electrophoretic means for 2 hours at 60 volts. The membrane was pretreated for one hour in PBS/0.1% Tween 20 with 5% non-fat dry milk. After washing 3 times in 15 PBS/Tween buffer, the membrane was incubated with a 1:2000 dilution of a monospecific antiserum to PGHS-2 or a 1:1000 dilution of an antiserum to PGHs-1 in PBS/Tween with 1% BSA for one hour with continuous shaking. The membrane was washed 3X in PBS/Tween and then incubated with a 1:3000 dilution of horseradish 20 peroxidase conjugated donkey antiserum to rabbit Ig (Amersham) in PBS/Tween with 1% BSA for one hour with continuous shaking. The membrane was then washed 3X in PBS/Tween and the ECL immunodetection system (Amersham) was used to detect the level of expression of prostaglandin endoperoxide synthases-2.

20

### RESULTS:

The following compounds were tested and found to be active (inhibited LPS induced PGHS-2 protein expression in rank order potency similar to that for inhibiting cytokine production as noted in assays indicated):

25 6-(4-Fluorophenyl)-2,3-dihydro-5-(4-pyridinyl)imidazo[2,1-b]thiazole and Dexamethasone

Several compounds were tested and found to be inactive (up to 10µM): 2-(4-Methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-(5H)-pyrrolo[1,2-a]imidazole rolipram, phenidone and NDGA.

30 None of the compounds tested was found to inhibit PGHS-1 or cPLA<sub>2</sub> protein levels in similar experiments.

### SYNTHETIC EXAMPLES

The invention will now be described by reference to the following examples 35 which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, all solvents are highest available purity and all reactions run under anhydrous conditions in an argon atmosphere unless otherwise indicated.

In the Examples, all temperatures are in degrees Centigrade (°C). Mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated.  $^1\text{H}$ -NMR (hereinafter "NMR") spectra were recorded at 250 MHz using a Bruker AM 250 or Am 400 spectrometer. Multiplicities indicated are: 5 s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br indicates a broad signal. Sat. indicates a saturated solution, eq indicates the proportion of a molar equivalent of reagent relative to the principal reactant.

Flash chromatography is run over Merck Silica gel 60 (230 - 400 mesh).

10

### Example 1

#### 1-[3-(4-Morpholinyl)propyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole

##### a) 4-fluorophenyl-tolylthiomethylformamide

A solution of p-fluorobenzaldehyde (13.1 milliliters (hereinafter mL), 122 millimoles (hereinafter mmol) thiocresol (16.64 grams (hereinafter g), 122 mmol), 15 formamide (15.0 mL, 445 mmol), and toluene (300 mL) were combined and heated to toluene reflux with azeotropic removal of  $\text{H}_2\text{O}$  for 18 h. The cooled reaction was diluted with EtOAc (500 mL) and washed with satd aq  $\text{Na}_2\text{CO}_3$  (3 x 100 mL), satd aq NaCl (100 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The residue was triturated with petroleum ether, filtered and dried in vacuo to afford 28.50 g of the title compound as a 20 white solid (85 %). melting point (hereinafter mp) = 119 - 120°.

##### b) 4-fluorophenyl-tolylthiomethylisocyanide

The compound of example 1(a) (25 g, 91 mmol) in  $\text{CH}_2\text{Cl}_2$  (300 mL) was cooled to -30° and with mechanical stirring  $\text{POCl}_3$  (11 mL, 110 mmol) was added dropwise followed by the dropwise addition of  $\text{Et}_3\text{N}$  (45 mL, 320 mmol) with the 25 temperature maintained below -30°. Stirred at -30° for 30 min and 5° for 2 h, diluted with  $\text{CH}_2\text{Cl}_2$  (300 mL) and washed with 5% aq  $\text{Na}_2\text{CO}_3$  (3 x 100 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to 500 mL. This solution was filtered through a 12 x 16 cm cylinder of silica in a large sintered glass funnel with  $\text{CH}_2\text{Cl}_2$  to afford 12.5 g (53%) of purified isonitrile as a light brown, waxy solid. IR ( $\text{CH}_2\text{Cl}_2$ ) 2130  $\text{cm}^{-1}$ .

30

##### c) Pyridine-4-carboxaldehyde-[4-Morpholinylprop-3-yl]imine

Pyridine-4-carboxaldehyde (2.14 g, 20 mmol), 4-(3-aminopropyl)morpholine (2.88 g, 20 mmol), toluene (50 mL) and  $\text{MgSO}_4$  (2 g) were combined and stirred under argon for 18 h. The  $\text{MgSO}_4$  was filtered off and the filtrate was concentrated and the residue was reconcentrated from  $\text{CH}_2\text{Cl}_2$  to afford 4.52 g (97%) of the title compound 35 as a yellow oil containing less than 5% of aldehyde based on  $^1\text{H}$  NMR.  $^1\text{H}$  NMR ( $\text{CD}_3\text{Cl}$ ): d 8.69 (d,  $J$  = 4.5 Hz, 2H), 8.28 (s, 1H), 7.58 (d,  $J$  = 4.5 Hz, 2H), 3.84 (m, 6H), 2.44 (m, 6H), 1.91 (m, 2H).

##### d) 1-[3-(4-Morpholinyl)propyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole

The compound of example 1(b) (1.41 g, 5.5 mmol), and the compound of example 1(c) (1.17 g, 5.0 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (10 mL) were cooled to 5 °C. 1,5,7-triazabicyclo[4.4.0]dec-5-ene, henceforth referred to as TBD, (0.71 g 5.0 mmol) was added and the reaction was kept at 5 °C for 16 h, diluted with EtOAc (80 mL) and washed with satd aq Na<sub>2</sub>CO<sub>3</sub> (2 x 15 mL). The EtOAc was extracted with 1 N HCl (3 x 15 mL), and the acid phases were washed with EtOAc (2 x 25 mL), layered with EtOAc (25 mL) and made basic by the addition of solid K<sub>2</sub>CO<sub>3</sub> til pH 8.0 and then 10% NaOH til pH 10. The phases were separated and the aq was extracted with additional EtOAc (3 x 25 mL). The extracts were dried (K<sub>2</sub>CO<sub>3</sub>) concentrated and the residue was 10 crystallized from acetone/hexane to afford 0.94 g (51%) of the title compound. mp = 149 - 150 °.

### Example 2

15 5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-(1,3-dioxycyclopentyl)cyclohexyl)imidazole

a) 1-Amino-4-(1,3-dioxycyclopentyl)cyclohexane 1,4-Cyclohexanedione monoethylene ketal (15.6 g, 0.10 mol) H<sub>2</sub>O (170 mL) and Na<sub>2</sub>CO<sub>3</sub> (27.8 g) were combined and NH<sub>2</sub>OH • HCl (27.8 g, 0.40 mol) was added in small portions. The resulting mixture was stirred for 30 min. Extraction with EtOAc, drying (Na<sub>2</sub>SO<sub>4</sub>) and 20 concentration afforded 17.1 g (100%) of 4-(1,3-dioxycyclopentyl)-cyclohexanone oxime.

The oxime (6.0 g, 35 mmol), Raney Ni (ca 3 mL as a suspension in pH 7.0 H<sub>2</sub>O) and EtOH (abs) were combined and shaken at 50 psi H<sub>2</sub> for 16 h. The catalyst was filtered off and the filtrate was concentrated and distilled to afford 2.4 g (60%) of the title compound (bp = 68°, 0.18 mm).

25 b) 2-Aminopyrimidine-4-carboxaldehyde (4-ethylene ketal-1-cyclohexyl) imine

The product of the previous step 2 (a), and the product of Example 3 (b), prepared below, were reacted by the procedure of 1(c) except that the solvent was CH<sub>2</sub>Cl<sub>2</sub> and no drying agent (MgSO<sub>4</sub>) was required to afford the title compound as a yellow oil.

30 c) 5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-dioxycyclohexyl)imidazole

Following the procedure of example 1(d) except using the compound of the previous step as the imine afforded the title compound. ESI mass spectrum MH<sup>+</sup> = 396.

### Example 3

35 2-Aminopyrimidine-4-carboxaldehyde

a) 2-Aminopyrimidine-4-carboxaldehyde dimethyl acetal

Dimethylformamide dimethyl acetal (55 mL, 0.41 mol), and pyruvic aldehyde dimethyl acetal (50 mL, 0.41 mol) were combined and heated to 100° for about 18 hours. Methanol was removed in vacuo to afford an oil.

5 A solution of NaOH (18 g, 0.45 mol) in H<sub>2</sub>O (50 mL) was added to guanidine HCl (43 g, 0.45 mol) in H<sub>2</sub>O (100 mL), and the resulting solution was added to the above described oil. The resulting mixture was stirred at 23° for 48 h. Filtration afforded 25g (50%) of the title compound.

b) 2-Aminopyrimidine-4-carboxaldehyde

10 The compound of the previous step (1.69 g, 10 mmol) and 3N HCl (7.3 mL, 22 mmol) were combined and heated to 48° for 14h, cooled, layered with EtOAc (50 mL) and neutralized by the addition of NaHCO<sub>3</sub> (2.1g, 25 mmol) in small portions. The aq phase was extracted with EtOAc (5 x 50 mL) and the extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford 0.793 g (64%) of the title compound.

15 Example 4

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-ketocyclohexyl)imidazole

20 The product of example 2 (1.27 g, 3.22 mmol) and 3 N HCL (12.4 mL) were combined and stirred at 23° for 16 h, combined with 10% aq Na<sub>2</sub>CO<sub>3</sub> (50 mL) and extracted with EtOAc. The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated and flash chromatographed (0 - 4% MeOH) to afford 0.72 g (64%) of the title compound as a white solid. ESI mass spectrum MH<sup>+</sup> = 352.

Example 5

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-cyclohexyl oxime) imidazole

25 The product of example 4 (351 g, 1.0 mmol), NH<sub>2</sub>OH • HCl (278 mg, 4.0 mmol), H<sub>2</sub>O (6 mL), and CH<sub>3</sub>OH, (2 mL) were combined, Na<sub>2</sub>CO<sub>3</sub> (278 mg, 2.6 mmol) was added in small portions. The mixture was stirred for 24 h, aq NaHCO<sub>3</sub> was added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>, concentrated and flash chromatographed with 0 - 8% MeOH to afford 0.248 g (67%) of the title compound.

30

Example 6

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-cyclohexyl hydroxylamine) imidazole

35 The product of example 5 (250 mg, 0.68 mmol), NaCNBH<sub>3</sub> (42 mg, 0.68 mmol) and MeOH (2.5 mL) were combined. Methanolic HCl (several drops) was added (pH < 3) and the mixture was stirred for 1 h, diluted with 10% aq NaOH and extracted with EtOAc. The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) concentrated and flash chromatographed (0 - 8% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to afford 160mg (64%). ESI mass spectrum MH<sup>+</sup> = 369.

Example 75-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(*trans*-4-hydroxyurea) imidazole and  
5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(*cis*-4-hydroxyurea) imidazole

5 The product of example 6 was reacted by the procedure of Adams et al (WO 91/14674 published 3 October 1991) to afford a mixture of *cis* and *trans* cyclohexyl hydroxyurea isomers. Trituration of the mixture with CH<sub>2</sub>Cl<sub>2</sub> selectively dissolved the *cis* isomer (based on nmr). The solid was filtered off. The filtrate was concentrated to afford 5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(*cis*-4-hydroxyurea) imidazole

10 SB 223768. containing ca 20% of the *trans* isomer based on nmr. mp = 185 - 245 (dec).

The solid obtained above was redissolved in CH<sub>2</sub>Cl<sub>2</sub>/MeOH and concentrated until precipitation began. Filtration afforded pure 5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(*trans*-4-hydroxyurea) imidazole. mp = 188 - 190°.

15

Example 85-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(*trans*-4-hydroxycyclohexyl) imidazole

The product of example 4 (0.61 g, 1.74 mmol) and 1M NaBH<sub>4</sub> in CH<sub>3</sub>OH were combined in CH<sub>3</sub>OH / THF (1:1, 7 mL) and stirred for 10 min, the reaction was poured into 10% aq Na<sub>2</sub>CO<sub>3</sub> (25 mL), extracted with EtOAc (4 x 50 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). Flash chromatography (0 - 8% CH<sub>3</sub>OH in CH<sub>2</sub>Cl<sub>2</sub>) afforded 0.52 g (85%) of the title compound.

25 In methods analagous to those described above and in the schematics herein the following compound may be prepared:

Example 9: 5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-aminocyclohexyl)imidazole.

Example 10

30 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-ketocyclohexyl)imidazole

a) 2-N-methylaminopyrimidine-4-carboxaldehyde

The title compound was prepared as described in Example 3 using methyl guanidine·HCl. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 9.95 (s, 1H), 8.88 (d, 1H), 7.50 (, 1H), 3.54 (s, 3H), 2.54 (s, 3H).

35 b) 2-N-methylaminopyrimidine-4-carboxaldehyde-(4-ethyleneketal-1-cyclohexyl)imine

The compound of example 10(a) (.8 g, 5.8 mmol) and the compound of example 2(a) (.8 g, 5.1 mmol) were stirred for 18 h. in DMF (12 mL). Concentration under

vacuum afforded the title compound as a yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.34 (d, 1H), 8.15 (s, 1H), 7.13 (d, 1H), 5.25 (d, 1H), 3.39 (m, 1H), 3.03 (d, 3H), 1.90 (m, 7H), 1.79 (m, 2H), 1.65 (m, 2H).

c) 4-fluorophenyl-tolylsulfonylmethyl formamide

Concentrated HCl (15 mL) was added dropwise to a suspension of *p*-toluene sulfinic acid sodium salt (30 g) in  $\text{H}_2\text{O}$  (100 mL) and *tert*-butyl methyl ether (50 mL). After stirring for 15 min., the organic phase was removed and the aqueous phase was extracted with *tert*-butyl methyl ether. The organic phases were combined, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated almost to dryness. Hexane was added and the resulting solid was filtered to give the free acid (22.06 g). The free acid (140.6 mmol) was combined with *p*-fluorobenzaldehyde (22 mL, 206 mmol), formamide (20 mL, 503 mmol) and camphor sulfonic acid (4 g, 17.3 mmol) and stirred at 60 °C for 18 h. The resulting solid was broken up and stirred with methanol (35 mL), and hexane (82 mL). The mixture was filtered. The large chunks were crushed and the resulting solid was stirred vigorously .5 h. in methanol/hexane (200 mL, 1:3). The suspension was filtered to afford the title compound (27.08 g, 62.7% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.13 (s, 1H), 7.71 (d, 2H), 7.43 (dd, 2H), 7.32 (d, 2H), 7.08 (t, 2H), 6.35 (d, 1H), 2.45 (s, 3H).

d) 4-fluoro-tolylsulfonylmethyl isocyanide

A mixture of the compound from example 10(c) (2.01 g, 6.52 mmol) in ethylene glycol dimethyl ether (DME) (32 mL) was cooled to -10°C. Added dropwise was  $\text{POCl}_3$  (1.52 mL, 16.30 mmol) dissolved in DME (3 mL) keeping the internal temperature below -5°C. After stirring at -5°C for 1 h., the reaction was quenched with  $\text{H}_2\text{O}$  and the product was extracted with EtOAc followed by an aqueous saturated  $\text{NaHCO}_3$  wash. The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue was triturated with petroleum ether and filtered affording the title compound (1.70 g, 90% yield) as an orange brown solid. IR ( $\text{CH}_2\text{Cl}_2$ ) 2135  $\text{cm}^{-1}$ .

e) 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-(1,3-dioxycyclopentyl)cyclohexyl]imidazole

The compound from example 10(b) (1.6 g, 5.84 mmol) was combined with the compound from example 10(d) (2 g, 6.9 mmol) and powdered  $\text{K}_2\text{CO}_3$  (1.2 g, 8.7 mmol) in DMF (12 mL) at 0°C for 3 h. The mixture was slowly warmed to room temperature and stirred an additional 18 h. EtOAc was added and the mixture was filtered, concentrated and taken up in  $\text{H}_2\text{O}$ /EtOAc. The resulting yellow solid was filtered and purified by flash chromatography (silica gel) eluting with 5%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  to afford the title compound (.50 g, 29% yield)  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.16 (d, 1H), 7.78 (s, 1H), 7.45 (q, 2H), 6.99 (t, 2H), 6.40 (d, 1H), 5.70 (m,



1H), 4.74 (m, 1H), 3.99 (s, 4H), 3.05 (d, 3H), 2.20 (M, 2H), 2.04 (q, 2H), 1.89 (dd, 2H), 1.68 (m, 3H).

f) 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-ketocyclohexyl)imidazole

5 Following the procedure of example 4 except using the compound of example 10(e) (.50 g, .22 mmol), the title compound was obtained (.37 g, 78% yield). mp 232.5 - 233.5°C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.97 (d, 1H), 7.69 (s, 1H), 6.89 (t, 2H), 6.24 (d, 1H), 5.08 (m, 1H), 3.25 (s, 1H), 2.91 (d, 3H), 2.39 (d, 5H), 2.08 (m, 2H), 1.92 (m, 1H).

10

Example 11

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(*trans*-4-hydroxycyclohexyl)imidazole

The title compound was prepared following the procedure of example 8 except 15 using the compound from example 11(f) (.49 g, 1.34 mmol) and recrystallizing from EtOH/H<sub>2</sub>O to afford white crystals (.38 g, 77% yield). mp 230 - 231°C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.08 (m, 1H), 7.70 (s, 1H), 7.37 (q, 2H), 6.98 (t, 2H), 6.32 (d, 1H), 4.67 (m, 1H), 3.67 (m, 1H), 3.00 (s, 3H), 2.18 (m, 2H), 2.07 (m, 2H), 1.75 (m, 2H), 1.37 (m, 2H).

20 Using an analogous methods to Example 11 the cis isomer was also obtained : 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(*cis* 4-hydroxycyclohexyl)imidazole

Example 12

5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-(*cis*-pyrrolidinyl)cyclohexyl]imidazole and 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-(*trans*-1-pyrrolidinyl)cyclohexyl]imidazole

To a solution of pyrrolidine (.3 mL, 3.6 mmol) in MeOH (3 mL) was added 5% 30 ethanolic HCl (.25 mL). The compound of example 10(f) (.50 g, 1.26 mmol) was added followed by sodium cyanoborohydride (.05 g, 1.30 mmol). After stirring for 2 days, the mixture was concentrated and the residue was suspended in H<sub>2</sub>O and brine and then extracted with EtOAc. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The products were purified by flash chromatography (silica gel) eluting with 5% - 20% MeOH/CH<sub>2</sub>Cl<sub>2</sub> with the *cis*- isomer eluting from the column first to afford the title compounds 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-*cis*-pyrrolidinyl)cyclohexyl]imidazole, mp 192 - 193°C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 35 8.04 (s, 1H), 7.95 (s, 1H), 7.35 (q, 2H), 6.95 (t, 2H), 6.30 (d, 1H), 4.59 (s, 1H), 3.40 (m, 1H), 2.97 (s, 3H), 2.58 (s, 4H), 2.13 (q, 2H), 2.00 (d, 2H), 1.84 (m, 6H), 1.50 (t, 2H), and 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-(*trans*-1-pyrrolidinyl)-

cyclohexyl]imidazole, mp 155 - 156°C,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.03 (d, 1H), 7.69 (s, 1H), 7.35 (q, 2H), 6.95 (t, 2H), 6.28 (d, 1H), 4.61 (t, 1H), 3.12 (s, 1H), 2.96 (s, 3H), 2.58 (s, 4H), 2.25-2.05 (m, 4H), 1.78 (s, 4H), 1.70 (m, 2H), 1.35 (t, 2H).

5

Example 135-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-ethynyl-4-hydroxycyclohexyl)imidazole

The compound from example 10(f) (.50 g, 1.37 mmol) was suspended in dry THF (5 mL) and cooled to -78°C. Ethynylmagnesium bromide (13.4 mL, 6.17 mmol, .5 M in THF) was added and the mixture was stirred for 2 h. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the product was extracted with  $\text{EtOAc}$ . The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The product was purified by flash chromatography (silica gel) eluting with 2%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  to afford the title compound. mp 233.5 - 234.5°C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.08 (d, 1H), 7.77 (s, 1H), 7.38 (q, 2H), 6.97 (t, 2H), 6.31 (d, 1H), 4.68 (s, 1H), 2.76 (s, 3H), 2.62 (s, 1H), 2.10 (m, 6H), 1.63 (q, 2H).

Example 145-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-amino-4-methylcyclohexyl)imidazolea) 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-methylcyclohexyl)imidazole

Following the procedure of example 13 except using methylmagnesium bromide, the title compound was obtained (76% yield) as a 1:1 mixture of *cis*- and *trans*- isomers.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.13 (s, 1H), 7.79 (s, .5 H), 7.72 (s, .5H), 7.43 (m, 2H), 6.96 (m, 2H), 6.38 (m, 1H), 5.45 (m, 1H), 4.68 (m, .5H), 4.52 (m, .5H), 3.00 (d, 3H), 2.30-1.40 (m, 8H), 1.36 (s, 1.5 H), 1.25 (s, 1.5H).

b) 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-amino-4-methylcyclohexyl)imidazole

A mixture of the compound from example 14(a) (.28 g, .75 mmol), sodium cyanide (.03 g) and  $\text{H}_2\text{SO}_4$  (.5 mL) was stirred for 18 h. After diluting with  $\text{H}_2\text{O}$  and adding 50%  $\text{NaOH}$ , the mixture was refluxed for 4 h., then cooled and extracted with  $\text{EtOAc}$ . The aqueous phase was made basic with 50%  $\text{NaOH}$  and was extracted with  $\text{EtOAc}$ . The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue was purified by flash chromatography (silica gel) eluting with  $\text{MeOH}/\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$  (20:80:2) to afford the title compound. mp 186 - 192°C.

Example 15

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-acetamido-4-methylcyclohexyl)imidazole

A mixture of the compound of example 14(b) (.02 g, .05 mmol) and DMAP (.0012 g, .01 mmol) in pyridine (1 mL) was cooled to 0°C. Acetic anhydride (.009 mL) was added and the mixture was warmed to room temperature. After stirring for 18 h., the mixture was diluted with H<sub>2</sub>O and the product was extracted with EtOAc. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Flash chromatography (silica gel) eluting with 0% - 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> afforded the title compound (.019 g, 90% yield). mp 175 - 176°C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.14 (d, 1H), 7.77 (s, 1H), 7.43 (q, 2H), 7.00 (t, 2H), 6.40 (d, 1H), 4.58 (m, 1H), 3.03 (d, 3H), 2.41 (d, 2H), 2.09 (m, 2H), 2.02 (s, 3H), 1.82 (m, 2H), 1.40 (c, 3H), 1.37 (m, 2H).

In methods analogous to Examples 1 to 15 above the following compounds may be made:

15 Example 16 : 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-methylcyclohexyl)imidazole; m.p. 160-161°C.

Example 17 : 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-oxiranyl-cyclohexyl)imidazole; m.p. 229-230°C

20

Example 18

5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-cyanomethyl-4-hydroxycyclohexyl)imidazole

a) 4-Fluorophenyl-tolylsulfonylmethylformamide

To a suspension of p-toluenesulfonic acid sodium salt (30 g) in H<sub>2</sub>O (100 mL) was added methyl t-butyl ether (50 mL) followed by dropwise addition of conc. HCl (15 mL). After stirring 5 min., the organic phase was removed and the aqueous phase was extracted with methyl t-butyl ether. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to near dryness. Hexane was added and the free acid was filtered.

30

The p-toluenesulfonic acid (22 g, 140.6 mmol), p-fluorobenzaldehyde (22 mL, 206 mmol), formamide (20 mL, 503 mmol) and camphor sulphonic acid (4 g, 17.3 mmol) were combined and stirred at 60°C 18 h. The resulting solid was broken up and stirred with a mixture of MeOH (35 mL) and hexane (82 mL) then filtered. The solid was resuspended in MeOH/hexane (1:3, 200 mL) and stirred vigorously to break up remaining chunks. Filtration afforded the title compound (27 g, 62 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.13 (s, 1H), 7.71 (d, 2H), 7.43 (dd, 2H), 7.32 (d, 2H), 7.08 (t, 2H), 6.34 (d, 1H), 2.45 (s, 3H).

b) 4-Fluorophenyl-tolylsulfonylmethylisocyanide

f) 2-N-Methylamino-4-carboxaldehyde(4-ethylene ketal cyclohexyl)imine

A mixture of the compound from the previous step (9.5 g, 6.9 mmol) and 1-amino-4-(1,3-dioxycyclopentyl)cyclohexane prepared in example 18 (c) (10.8 g, 6.9 mmol) were stirred in DMF (150 mL) 18 h. The title compound was used 5 without any purification.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.34 (d, 1H), 8.15 (s, 1H), 7.13 (d, 1H), 5.25 (d, 1H), 3.39 (m, 1H), 3.03 (d, 3H), 1.90 (m, 7H), 1.79 (m, 2H), 1.65 (m, 2H).

g) 5-[4-(2-N-Methylaminopyrimidinyl)-4-(4-fluorophenyl)-1-(4-ethylene ketal cyclohexyl)imidazole

10 To the crude product from the previous example in DMF cooled to 0°C was added 4-fluorophenyl-tolylsulfonylmethylisocyanide prepared in example 1 (b) (20 g, 69 mmol) and  $\text{K}_2\text{CO}_3$  (12 g, 87 mmol). The mixture was stirred at 0°C for 3 h. then gradually warmed to room temp. and stirred for 18 h. EtOAc was added and the mixture was filtered washing the solid with EtOAc.  $\text{H}_2\text{O}$  was added 15 to the filtrate and the organic phase was separated, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The residue was purified by flash chromatography (Silica gel, 2% MeOH/ $\text{CH}_2\text{Cl}_2$ ) to afford the title compound as a yellow solid (10.7 g, 38% yield).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.16 (d, 1H), 7.78 (s, 1H), 7.45 (q, 2H), 6.99 (t, 2H), 6.40 (d, 1H), 5.70 (m, 1H), 4.74 (m, 1H), 3.99 (s, 4H), 3.05 (d, 3H), 2.20 (m, 2H), 2.04 (dq, 2H), 1.89 (dd, 2H), 1.68 (m, 2H).

h) 5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-oxocyclohexyl)imidazole

20 A mixture of the compound from the previous step (10.73 g, 26.23 mmol) in 3N HCl (150 mL) was stirred 36 h. then neutralized with saturated aqueous  $\text{Na}_2\text{CO}_3$  and filtered. The solid was washed with water and the aqueous mixture was extracted with EtOAc. The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated giving the title compound as a pale yellow solid (7.9 g, 77% yield) mp 232.5 - 233.5°C.

i) 5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-oxiranylcyclohexyl)imidazole

30 To a suspension of sodium hydride (0.07 g, 1.18 mmol, 60% suspension in mineral oil) in DMSO (1.2 mL) was added trimethylsulfoxonium iodide (0.39 g, 1.78 mmol). The mixture was stirred until gas evolution ceased. Added to this was the compound from the previous step (0.50 g, 1.4 mmol) in dry THF (5 mL). 35 The resulting mixture was stirred 4 h. then poured into  $\text{H}_2\text{O}$  and filtered. The resulting solid was triturated with acetone/hexane to afford the title compound (.4117 g, 77% yield). mp 229 - 230°C.

j) 5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-cyanomethyl-4-hydroxycyclohexyl)imidazole

To a solution of the compound of from the previous step in dry THF (10 mL) was added diethylaluminum cyanide (2 mL, 1M in toluene). After stirring at 5 70°C for 1 h., the mixture was cooled and quenched with 10% NaOH and decanted. The organic phase was decanted then concentrated. The residue was purified by flash chromatography (silica gel, 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) and the product was recrystallized from EtOH/H<sub>2</sub>O affording the title compound as white crystals. mp 152 - 154°C.

10

Example 19

5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-hydroxymethylcyclohexyl)imidazole

a) A solution of the compound in example 18 (i) (0.084 g, .22 mmol) and 15 88% formic acid (3 mL) was stirred 1 h. The mixture was concentrated and the residue was dissolved in MeOH. Excess Et<sub>3</sub>N was added and the mixture was stirred 24 h. The mixture was concentrated and purified by flash chromatography (silica gel, 2% - 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>). The resulting white solid was triturated with acetone/hexane to afford the title compound as a mixture of cis and trans 20 isomers (0.047 g, 53% yield). mp 125 - 130°C.

Example 20

5-[4-(2-Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-hydroxy-4-(1-propynyl)cyclohexyl]imidazole

a) 2-Amino-4-carboxaldehyde(4-ethylene ketal cyclohexyl)imine

Following the procedure of example 18 (f) substituting 2-aminopyrimidine-4-carboxaldehyde (prepared in Example 3) afforded the title compound. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.36 (d, 1H), 8.16 (s, 1H), 7.21 (d, 1H), 5.13 (m, 30 1H), 3.98 (s, 4H), 2.00 - 1.40 (m, 8H).

b) 5-[4-(2-amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-ethylene ketal cyclohexyl)imidazole

Following the procedure of example 18(g) using the compound from the previous step afforded the title compound. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.29 (d, 1H), 7.77 (s, 1H), 7.45 (q, 2H), 7.00 (t, 2H), 6.50 (d, 1H), 5.12 (s, 2H), 4.63 (m, 1H), 4.00 (s, 4H), 2.17 (m, 2H), 2.05 (m, 2H), 1.90 (m, 2H), 1.73 (m, 2H).

c) 5-[4-(2-Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-oxocyclohexyl)imidazole

Following the procedure of example 1(h) except using the from the previous step afforded the title compound as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.02 (d, 1H), 7.74 (s, 1H), 7.32 (q, 2H), 6.94 (t, 2H), 6.28 (d, 1H), 5.10 (m, 1H), 2.93 (s, 3H), 2.44 (m, 6H), 2.12 (m, 2H).

5 d) 5-(Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-hydroxy-2-propynyl)cyclohexylimidazole

To a suspension of the compound from the previous step (0.49 g, 1.4 mmol) in dry THF (30 mL) at  $-78^\circ\text{C}$  was added propynyl magnesium bromide [15 mL, 1M sln. in THF, obtained by bubbling propyne gas (4 g) into dry THF (75 mL) followed by the addition of methyl magnesium bromide (26 mL, 78 mmol, 3M in  $\text{Et}_2\text{O}$ ) and stirring the mixture until gas evolution ceases]. The resulting mixture was gradually warmed to room temperature. After quenching with saturated aqueous  $\text{NH}_4\text{Cl}$ , the mixture was extracted with  $\text{EtOAc}$ . The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The resulting residue was purified by flash chromatography (silica gel, 5%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ) affording the title compound (0.068 g, 12% yield) as a white solid. mp 231 - 232°C.

Example 21

20 5-[4-(2-Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-methyl-cyclohexyl)imidazole

a) 5-[4-(2-Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-oxiranylcyclohexyl)imidazole

Following the procedure of example 18 (i) except using 5-[4-(2-amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-oxocyclohexyl)imidazole prepared in example 20 (c) afforded the title compound as a yellow solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.11 (d, 1H), 7.78 (s, 1H), 7.38 (q, 2H), 6.99 (t, 2H), 6.43 (d, 1H), 4.65 (m, 1H), 2.71 (s, 2H), 2.26 (m, 2H), 2.03 (m, 4H), 1.39 (m, 2H).

b) 5-[4-(2-Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-methylcyclohexyl)imidazole

30 To a suspension of the compound from the previous step (1.24 g, 3.39 mmol) in dry THF (40 mL) was added lithium aluminum hydride (5 mL, 5 mmol, 1M in THF). The resulting mixture was refluxed 1 h. then poured into 3N HCl (200 mL) and made basic with solid  $\text{NaHCO}_3$ . After extracting with  $\text{EtOAc}$ , the organic phase was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The resulting residue was purified by flash chromatography (silica gel, 5%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ) then crystallized from  $\text{EtOH}/\text{H}_2\text{O}$  to afford the title compound as a white solid (0.06 g, 4.8 % yield). mp 110 - 111°C.

In methods analogous to Examples 1 to 18 above the following compounds may be made:

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-isopropylcyclohexyl)imidazole;

5 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-phenylcyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-benzylcyclohexyl)imidazole;

10 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-cyanomethylcyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-(2-cyanoethyl)cyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-(2-aminoethyl)cyclohexyl)imidazole;

15 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-(2-nitroethyl)cyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxymethyl-4-amino-cyclohexyl)imidazole.

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-amino-cyclohexyl)imidazole;

20 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-amino-cyclohexyl)imidazole.

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-thiomethylcyclohexyl)imidazole.

25 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-hydroxymethylcyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-aminomethylcyclohexyl)imidazole;

5-[4-(2-amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-amino-4-methylcyclohexyl)imidazole;

30 5-[4-(2-amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-methylcyclohexyl)imidazole;

5-[4-(2-amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-oxiranyl-cyclohexyl)imidazole.

35

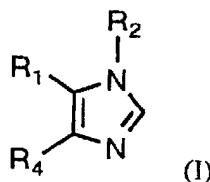
The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without

further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive 5 property or privilege is claimed are defined as follows.

What is Claimed Is:

1. A compound of the Formula

5



wherein

R<sub>1</sub> is 4-pyridyl, pyrimidinyl, quinolyl, isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl, which ring is optionally substituted with one or two substituents 10 each of which is independently selected from C<sub>1-4</sub> alkyl, halogen, hydroxyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylthio, C<sub>1-4</sub> alkylsulfinyl, CH<sub>2</sub>OR<sub>12</sub>, amino, mono and di- C<sub>1-6</sub> alkyl substituted amino, N(R<sub>10</sub>)C(O)R<sub>C</sub> or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>15</sub>;

R<sub>4</sub> is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted 15 by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, -C(Z)NR<sub>7</sub>R<sub>17</sub>, -C(Z)OR<sub>16</sub>, -(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>COR<sub>12</sub>, -SR<sub>5</sub>, -SOR<sub>5</sub>, -OR<sub>12</sub>, halo-substituted-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkyl, -ZC(Z)R<sub>12</sub>, -NR<sub>10</sub>C(Z)R<sub>16</sub>, or -(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>NR<sub>10</sub>R<sub>20</sub> and which, for other positions of substitution, is halogen, 20 cyano, -C(Z)NR<sub>13</sub>R<sub>14</sub>, -C(Z)OR<sub>3</sub>, -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>"COR<sub>3</sub>, -S(O)<sub>m</sub>R<sub>3</sub>, -OR<sub>3</sub>, halo-substituted-C<sub>1-4</sub> alkyl, -C<sub>1-4</sub> alkyl, -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>"NR<sub>10</sub>C(Z)R<sub>3</sub>, -NR<sub>10</sub>S(O)<sub>m</sub>'R<sub>8</sub>, -NR<sub>10</sub>S(O)<sub>m</sub>'NR<sub>7</sub>R<sub>17</sub>, -ZC(Z)R<sub>3</sub> or -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>"NR<sub>13</sub>R<sub>14</sub>;

v is 0, or an integer having a value of 1 or 2;

R<sub>25</sub> m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2,

m" is 0, or an integer having a value of 1 to 5;

R<sub>C</sub> is hydrogen, C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclyl, or heterocyclylC<sub>1-4</sub> alkyl C<sub>1-4</sub> alkyl

R<sub>30</sub> R<sub>2</sub> is an optionally substituted C<sub>3-7</sub> cycloalkyl, or C<sub>3-7</sub>cycloalkylC<sub>1-10</sub> alkyl;

R<sub>3</sub> is heterocyclyl, heterocyclylC<sub>1-10</sub> alkyl or R<sub>8</sub>;

R<sub>5</sub> is hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>7</sub>R<sub>17</sub>, excluding the moieties -SR<sub>5</sub> being -SNR<sub>7</sub>R<sub>17</sub> and -SOR<sub>5</sub> being -SOH;

R<sub>7</sub> and R<sub>17</sub> is each independently selected from hydrogen or C<sub>1-4</sub> alkyl or R<sub>7</sub> and R<sub>17</sub> 35 together with the nitrogen to which they are attached form a heterocyclic ring of 5 to

7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR15;

5 R<sub>8</sub> is C<sub>1</sub>-10 alkyl, halo-substituted C<sub>1</sub>-10 alkyl, C<sub>2</sub>-10 alkenyl, C<sub>2</sub>-10 alkynyl, C<sub>3</sub>-7 cycloalkyl, C<sub>5</sub>-7 cycloalkenyl, aryl, arylC<sub>1</sub>-10 alkyl, heteroaryl, heteroarylC<sub>1</sub>-10 alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NHS(O)<sub>2</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>13</sub>R<sub>14</sub>; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

n is an integer having a value of 1 to 10;

10 R<sub>9</sub> is hydrogen, -C(Z)R<sub>11</sub> or optionally substituted C<sub>1</sub>-10 alkyl, S(O)<sub>2</sub>R<sub>18</sub>, optionally substituted aryl or optionally substituted aryl-C<sub>1</sub>-4 alkyl;

R<sub>10</sub> and R<sub>20</sub> is each independently selected from hydrogen or C<sub>1</sub>-4 alkyl;

R<sub>11</sub> is hydrogen, or R<sub>18</sub>;

R<sub>12</sub> is hydrogen or R<sub>16</sub>;

R<sub>13</sub> and R<sub>14</sub> is each independently selected from hydrogen or optionally substituted 15 C<sub>1</sub>-4 alkyl, optionally substituted aryl or optionally substituted aryl-C<sub>1</sub>-4 alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>;

R<sub>15</sub> is hydrogen, C<sub>1</sub>-4 alkyl or C(Z)-C<sub>1</sub>-4 alkyl;

20 R<sub>16</sub> is C<sub>1</sub>-4 alkyl, halo-substituted-C<sub>1</sub>-4 alkyl, or C<sub>3</sub>-7 cycloalkyl;

R<sub>18</sub> is C<sub>1</sub>-10 alkyl, C<sub>3</sub>-7 cycloalkyl, heterocyclyl, aryl, arylC<sub>1</sub>-10 alkyl, heterocyclyl, heterocyclyl-C<sub>1</sub>-10alkyl, heteroaryl or heteroarylalkyl;

or a pharmaceutically acceptable salt thereof.

25 2. The compound according to Claim 1 wherein R<sub>1</sub> is an optionally substituted 4-pyridyl or 4-pyrimidyl.

30 3. The compound according to Claim 2 wherein the optional substituent is methyl, amino, or methlamino.

4. The compound according to Claim 2 wherein R<sub>4</sub> is an optionally substituted phenyl.

35 5. The compound according to Claim 4 wherein the phenyl is substituted one or more times independently by halogen, -SR<sub>5</sub>, -S(O)R<sub>5</sub>, -OR<sub>12</sub>, halo-substituted-C<sub>1</sub>-4 alkyl, or C<sub>1</sub>-4 alkyl.

6. The compound according to Claim 1 wherein R<sub>2</sub> is selected from optionally substituted C<sub>4</sub> to C<sub>7</sub>cycloalkyl.

7. The compound according to Claim 6 wherein R<sub>2</sub> is selected from optionally substituted C<sub>4</sub> or C<sub>6</sub> cycloalkyl or C<sub>4</sub> or C<sub>6</sub> cycloalkylC<sub>1-4</sub> alkyl.

8. The compound according to Claim 6 wherein the cycloalkyl ring may substituted one to three times independently by halogen; hydroxy; C<sub>1-10</sub> alkoxy; S(O)<sub>m</sub>C<sub>1-10</sub>alkyl, wherein m is 0, 1, or 2; amino; cyano, nitro; NR<sub>7</sub>R<sub>17</sub> group; C<sub>1-10</sub> alkyl; substituted alkyl wherein the substituents are selected from halogen, hydroxy, nitro, cyano, NR<sub>7</sub>R<sub>17</sub>, S(O)<sub>m</sub> C<sub>1-4</sub>alkyl, C(O)OR<sub>11</sub>; -O-(CH<sub>2</sub>)<sub>s</sub>O-, and s is 1 to 3; -C(O)H; =O; =N-OR<sub>11</sub>; -N(OR<sub>5</sub>)-OH; -N(OR<sub>5</sub>)-C(O)-R<sub>6</sub>; optionally substituted aryl; or optionally substituted arylalkyl; N(R<sub>10</sub>)C(O)X<sub>1</sub>; C(O)OR<sub>11</sub>; optionally substituted alkylene; or optionally substituted C<sub>1-10</sub>alkynyl;

15 wherein R<sub>5</sub> is hydrogen, a pharmaceutically acceptable cation, aroyl or a C<sub>1-10</sub> alkanoyl group;

R<sub>6</sub> is NR<sub>19</sub>R<sub>21</sub>; alkyl 1-6; halosubstituted alkyl 1-6; hydroxy substituted alkyl 1-6; alkenyl 2-6; aryl or heteroaryl optionally substituted by halogen, alkyl 1-6, halosubstituted alkyl 1-6, hydroxyl, or alkoxy 1-6;

20 R<sub>19</sub> is H or alkyl 1-6; and

R<sub>21</sub> is H, alkyl 1-6, aryl, benzyl, heteroaryl, alkyl substituted by halogen or hydroxyl, or phenyl substituted by a member selected from the group consisting of halo, cyano, alkyl 1-12, alkoxy 1-6, halosubstituted alkyl 1-6, alkylthio, alkylsulphonyl, or alkylsulfinyl; or R<sub>19</sub> and R<sub>21</sub> may together with the nitrogen to which they are attached 25 form a ring having 5 to 7 members, which members may be optionally replaced by a heteroatom selected from oxygen, sulfur or nitrogen; and

X<sub>1</sub> is C<sub>1-4</sub> alkyl, aryl or arylC<sub>1-4</sub>alkyl; N(R<sub>10</sub>)C(O) aryl.

9. The compound according to Claim 8 wherein the optional substituents are

30 hydroxy, aryl, arylalkyl, alkyl, alkynyl, NR<sub>7</sub>R<sub>17</sub>, NR<sub>7</sub>R<sub>17</sub> C<sub>1-6</sub> alkyl, =O, =NOR<sub>11</sub>, -NH(OH), -N(OH)-C(O)-NH<sub>2</sub>, cyanoalkyl, nitroalkyl, or -O-(CH<sub>2</sub>)<sub>2</sub>O-.

10. The compound according to Claim 1 which is:

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-(1,3-dioxycyclopentyl) cyclohexyl)

35 imidazole;

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-ketocyclohexyl)imidazole;

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-cyclohexyl oxime) imidazole;

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-cyclohexyl hydroxylamine) imidazole;

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(*trans*-4-hydroxyurea) imidazole;

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(*cis*-4-hydroxyurea) imidazole;

5 5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-hydroxycyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-ketocyclohexyl)-imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(*trans*-4-hydroxycyclohexyl)imidazole;

10 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(*cis*-4-hydroxycyclohexyl)imidazole;

5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-(*cis*-pyrrolidinyl)-cyclohexyl]imidazole;

15 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-(*trans*-1-pyrrolidinyl)-cyclohexyl]imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-ethynyl-4-hydroxycyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-(1-propynyl)-4-hydroxycyclohexyl)imidazole;

20 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-amino-4-methylcyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-acetamido-4-methylcyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-methylcyclohexyl)imidazole;

25 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-oxiranyl-cyclohexyl)imidazole;

5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-cyanomethyl-4-hydroxycyclohexyl)imidazole;

30 5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-hydroxymethylcyclohexyl)imidazole;

5-[4-(2-Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-hydroxy-4-(1-propynyl)-cyclohexyl]imidazole;

5-[4-(2-Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-methylcyclohexyl)imidazole; or a pharmaceutically acceptable salt thereof.

35

11. A pharmaceutical composition comprising a compound according to any of Claims 1 to 10 and a pharmaceutically acceptable carrier or diluent.

12. A method of treating a cytokine mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) according to any of Claims 1 to 10.

5

13. The method according to claim 11 wherein the mammal is afflicted with a cytokine mediated disease selected from rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic condition, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejection, Crohn's disease, ulcerative colitis or pyresis.

15

14. The method according to Claim 12 wherein the disease state is mediated by IL-1, IL-6, IL-8, or TNF.

15. The method according to Claim 13 wherein the cytokine mediated disease state is asthma, osteoporosis or arthritis.

20

16. A method of treating inflammation in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) according to any of Claims 1 to 10.

25

17. A method of treating osteoporosis in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) according to any of Claims 1 to 10.

30

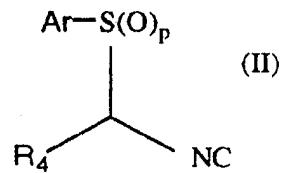
18. A method of treating a CSBP/RK/p38 kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) according to any of Claims 1 to 10.

35

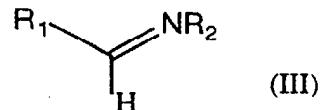
19. The method according to claim 18 wherein the mammal is afflicted with a CSBP/RK/p38 kinase mediated disease which is rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic condition, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease,

osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, Crohn's disease, ulcerative colitis or pyresis.

20. A process for preparing a compound of Formula (I) as defined in Claim 1 which  
5 comprises reacting a compound of the Formula (II) :



with a compound of the Formula (III):



10

wherein p is 0 or 2; and a base strong enough to deprotonate the isonitrile moiety of Formula (II);

15 and R<sub>1</sub>, R<sub>2</sub> and R<sub>4</sub> are as defined in Claim 1 or are precursors of the groups R<sub>1</sub>, R<sub>2</sub> and R<sub>4</sub> and Ar is an optionally substituted phenyl group, and thereafter if necessary, converting a precursor of R<sub>1</sub>, R<sub>2</sub> and R<sub>4</sub> to a group R<sub>1</sub>, R<sub>2</sub> and R<sub>4</sub>.

20

19. The process according to Claim 18 wherein the reaction, when p=0, utilizes TBD as a base.

25

20. The process according to Claim 18 wherein the reaction, when p=2, the base is an amine, a carbonates, a hydride, or an alkyl or aryl lithium reagent.

25

21. The process according to Claim 18 wherein the imine of Formula (III), is isolated prior to reaction with Formula (II).

22. The process according to Claim 18 wherein the imine of Formula (III), is formed in situ prior to reaction with Formula (II).

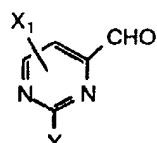
30

23. The process according to Claim 22 wherein the imine is formed in situ by reacting an aldehyde of the formula R<sub>4</sub>CHO, wherein R<sub>4</sub> is as defined for Formula (I), with a primary amine of the formula R<sub>2</sub>NH<sub>2</sub>, wherein R<sub>2</sub> is as defined for Formula (I).

24. The process according to Claim 22 wherein formation of the imine in situ utilizes dehydrating conditions.

25. The process according to Claim 23 wherein the solvent is N,N-dimethyl-  
5 formamide (DMF), halogenated solvents, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), alcohols, benzene, or toluene, or DME.

26. The process according to Claim 23 wherein the aldehyde R<sub>4</sub>CHO is a pyrimidine aldehyde of the formula:



10

wherein

X is NHR<sub>a</sub> and X<sub>1</sub> is defined as the optional substituent group on the R<sub>1</sub> moiety in Formula (I) according to Claim 1, to yield a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

15

27. The process according to Claim 23 wherein the primary amine R<sub>2</sub>NH<sub>2</sub> is a C<sub>3</sub>-7 cycloalkyl amine, C<sub>3</sub>-7 cycloalkyl C<sub>1</sub>-10alkyl amine, all of which may be optionally substituted.

20

28. The process according to Claim 27 wherein R<sub>2</sub> moiety of the R<sub>2</sub> is 4-hydroxycyclohexyl, 4-hydroxycyclohexyl, 4-ketocyclohexyl, 4-oxiranylhexyl, 4-methyl-4-hydroxy cyclohexyl, 4-isopropyl-4-hydroxy cyclohexyl, 4-pyrrolinindyl-cyclohexyl, 4-methyl-4-aminocyclohexyl, 4-methyl-4-acetamidocyclohexyl, 4-phenyl-4-hydroxy cyclohexyl, 4-benzyl-4-hydroxy cyclohexyl, 1-propenyl-4-hydroxy, 4-hydroxy-4-amino-cyclohexyl, 4-aminomethyl-4-hydroxy cyclohexyl or 4-(1,3-dioxycyclopentyl) cyclohexyl.

29. The process according to Claim 23 wherein the compound of Formula (I) is:

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-ketocyclohexyl)imidazole;

30 5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-cyclohexyl oxime) imidazole;

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-cyclohexyl hydroxylamine) imidazole;

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(*trans*-4-hydroxyurea) imidazole;

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(*cis*-4-hydroxyurea) imidazole;

35 5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-hydroxycyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-ketocyclohexyl)-imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(*trans*-4-hydroxycyclohexyl)imidazole;

5 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(*cis*-4-hydroxycyclohexyl)imidazole;

5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-(*cis*-4-pyrrolidinyl)cyclohexyl]imidazole;

10 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-(*trans*-1-pyrrolidinyl)cyclohexyl]imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-ethynyl-4-hydroxycyclohexyl)imidazole;

15 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-(1-propynyl)-4-hydroxycyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-amino-4-methylcyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-acetamido-4-methylcyclohexyl)imidazole;

20 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-methylcyclohexyl)imidazole;

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-oxiranyl-cyclohexyl)imidazole;

5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-cyanomethyl-4-hydroxycyclohexyl)imidazole;

25 5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-hydroxymethylcyclohexyl)imidazole;

5-[4-(2-Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-hydroxy-4-(1-propynyl)cyclohexyl]imidazole;

5-[4-(2-Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-methylcyclohexyl)imidazole;

30 or a pharmaceutically acceptable salt thereof.

30. A method of inhibiting the synthesis of prostaglandin endoperoxide synthase-2 (PGHS-2) in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) according to Claim 1.

31. The method according to Claim 30 wherein inhibition of PGHS-2 is used in the prophylaxis or therapeutic treatment of edema, fever, algesia, neuromuscular pain, headache, cancer pain, or arthritic pain.

5 32. The method according to Claim 30 wherein the compound is :  
5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-(1,3-dioxycyclopentyl) cyclohexyl) imidazole;  
5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-ketocyclohexyl)imidazole;  
5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-cyclohexyl oxime) imidazole;  
10 5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-cyclohexyl hydroxylamine) imidazole;  
5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(*trans*-4-hydroxyurea) imidazole;  
5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(*cis*-4-hydroxyurea) imidazole;  
5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-hydroxycyclohexyl)imidazole;  
15 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-ketocyclohexyl)- imidazole;  
5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(*trans*-4-hydroxy- cyclohexyl)imidazole;  
5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(*cis*-4-hydroxy-  
20 cyclohexyl)imidazole;  
5-[4-(2-N-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-(*cis*-pyrrolidinyl)- cyclohexyl]imidazole;  
5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-(*trans*-1-pyrrolidinyl)- cyclohexyl]imidazole;  
25 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-ethynyl-4-hydroxy- cyclohexyl)imidazole;  
5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-(1-propynyl)-4- hydroxycyclohexyl)imidazole;  
5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-amino-4-methyl-  
30 cyclohexyl)imidazole;  
5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-acetamido-4-methyl- cyclohexyl)imidazole;  
5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-methyl- cyclohexyl)imidazole;  
35 5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-oxiranyl- cyclohexyl)imidazole;  
5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-hydroxy methylcyclohexyl)imidazole;

- 70 -

5-[4-(2-N-methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-cyanomethylcyclohexyl)imidazole

5-[4-(2-Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-[4-hydroxy-4-(1-propynyl)-cyclohexyl]imidazole;

5 5-[4-(2-Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-hydroxy-4-methylcyclohexyl)imidazole;

or a pharmaceutically acceptable salt thereof.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/01094

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/235.8, 256, 259, 275, 314, 307, 341, 397; 544/124, 139, 284, 331, 333; 546/144, 167, 278; 548/306.1, 343.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Aust. J. Chem., Volume 35, issued 1982, R.P. Soni, "Studies in Heterocyclics: Novel Synthesis of 4,5-Diarylimidazoles", pages 1493-1496, see page 1494 compounds (1) and (2).	1-19 and 30-32
A	US, A, 4,725,600 (TAKAYA ET AL) 16 February 1988, see entire document.	1-19 and 30-32
X	J. Org. Chem., Volume 42, Number 7, issued 1977, Leusen et al, "Base-Induced Cycloaddition of Sulfonylmethyl Isocyanides to C,N Double Bonds. Synthesis of 1,5-Disubstituted and 1,4,5-Trisubstituted Imidazoles from Aldimines and Imidoyl Chlorides", pages 1153-1159, see entire document.	20-29

Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be part of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Z" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search	Date of mailing of the international search report
01 MAY 1996	15 MAY 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer <i>Y.N. GUPTA</i> Y.N. GUPTA
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/US96/01094

A. CLASSIFICATION OF SUBJECT MATTER:  
IPC (6):

C07D 233/00, 235/02, 401/04, 403/04; A61K 31/44, 31/47, 31/415, 31/505

A. CLASSIFICATION OF SUBJECT MATTER:  
US CL :

514/235.8, 256, 259, 275, 314, 307, 341, 397; 544/124, 139, 284, 331, 333; 546/144, 167, 278; 548/306.1, 343.5